ATTACHMENTS TO EXHIBIT 3

EXHIBIT 3 WAS PREVOUSLY FILED AND LODGED UNDER SEAL TO PLAINTIFFS' CONTROVERTING STATEMENT OF FACTS IN OPPOSITION TO BARD'S MOTION FOR SUMMARY JUDGMENT REGARDING PREEMPTION [DOC. 7374]

EXHIBIT A

Second Supplement Expert Report David A. Kessler, M.D.

Para. 11 Footnote 1

EMERGO

How long it takes the US FDA to clear medical devices via the 510(k) process

An examination of 15,000 medical device applications cleared by the US Food and Drug Administration between 2012 and 2016.

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

FDA

March 2017

www.EmergoGroup.com

Executive Summary

Dear Reader:

Every year Emergo examines published data on medical devices cleared by the US Food and Drug Administration (FDA). The 15,000+ device clearances we analyzed went through the FDA's Premarket Notification program, more commonly known as the 510(k). This process applies to nearly all Class 2 devices, and less than 10% of Class 1 devices. We sorted all devices based on the date they were cleared by FDA, not the date they were submitted.

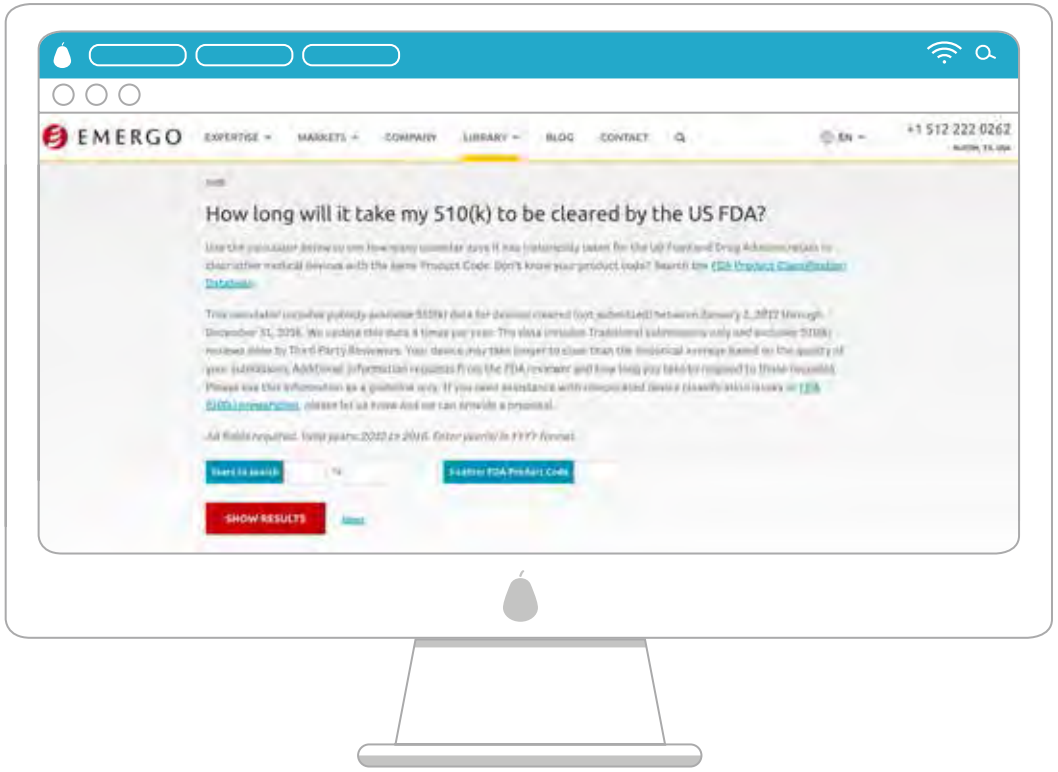
The intent of this analysis is to examine how long it took medical device manufacturers to get devices cleared by US FDA last year, look at trends and see which countries are submitting the most applications.

Throughout the analysis you will see references to "clearing" devices. Technically, the FDA does not "approve" medical devices for sale via the 510(k) process – they "clear" them for sale in the US. Thus, the term "clearance" is essentially synonymous with approval.

As always, we welcome your feedback on this report.

Regards,

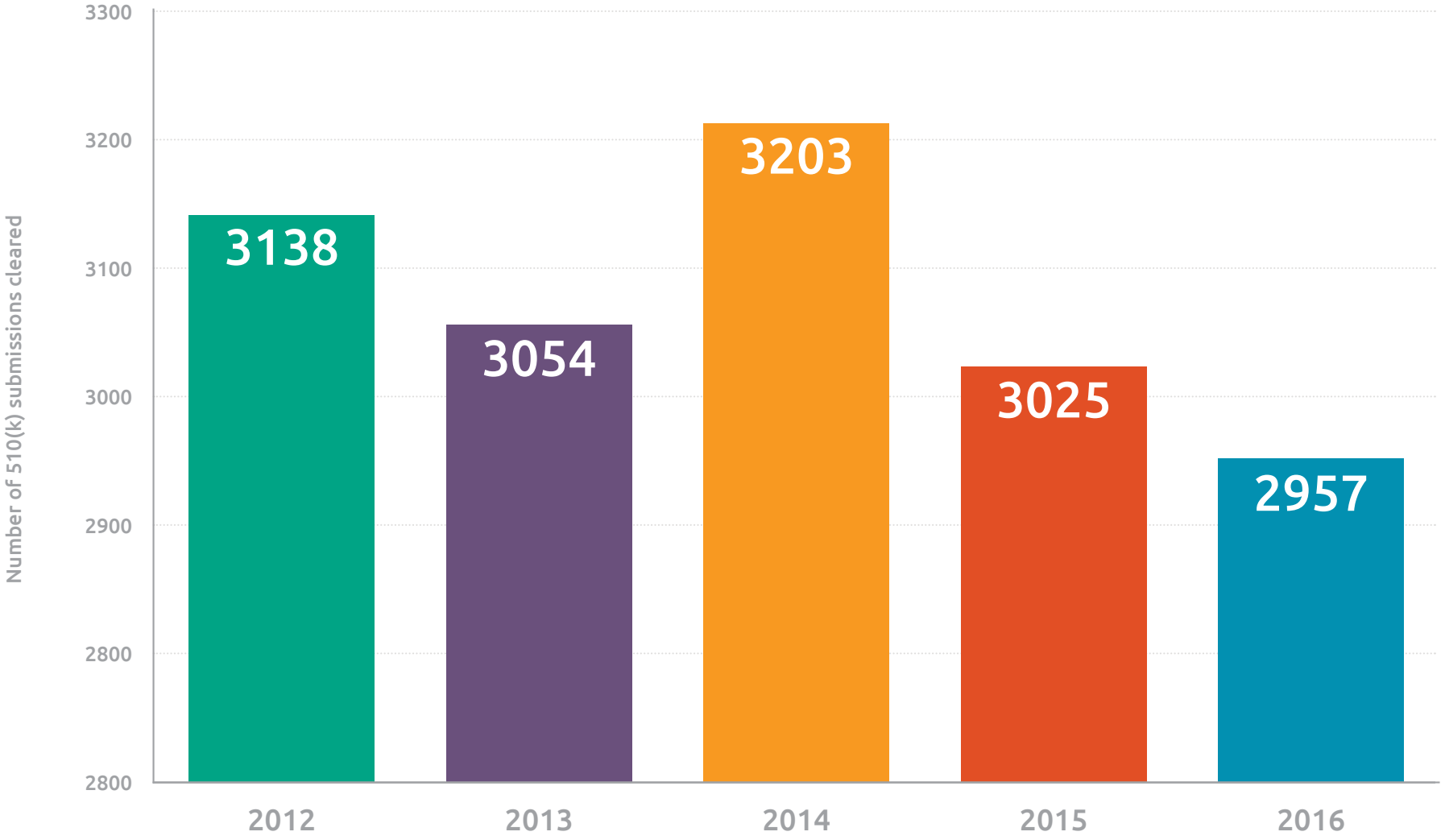
Chris Schorre
EMERGO | Vice President of Global Marketing
marketing@emergogroup.com



Be sure to try our FDA 510(k) calculator, which shows the average review time for specific devices cleared in the last five years.

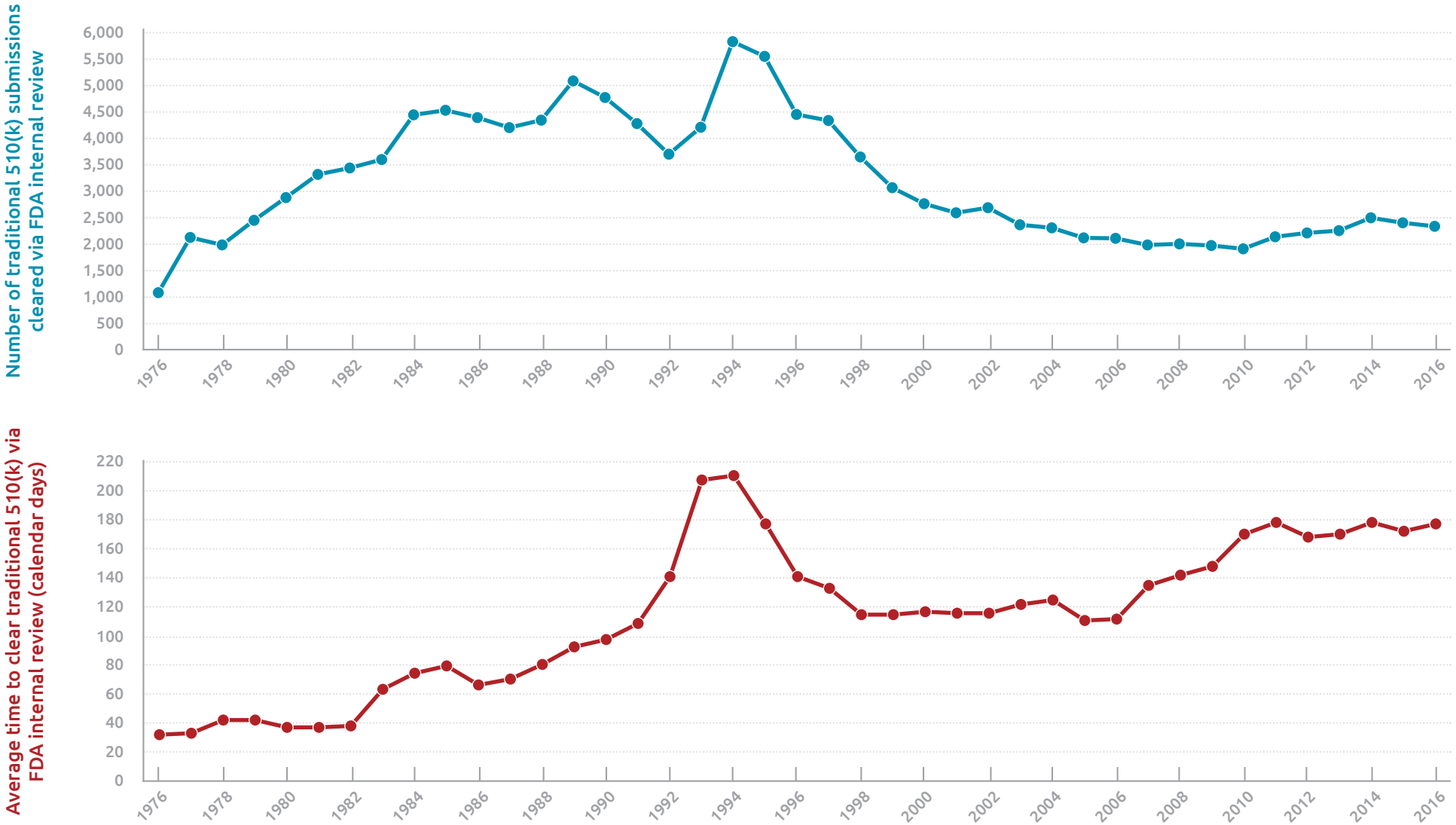
All FDA 510(k) submissions cleared - Traditional, Special, Abbreviated

Overall, the number of 510(k) submissions cleared in the US fell slightly in 2016. This represents the fewest number of devices cleared by the FDA since 2010 when roughly 2,800 devices were cleared. The decline is entirely attributable to fewer American companies submitting devices to the FDA, a decline which has been significant in 2015 and 2016 (see page 9).



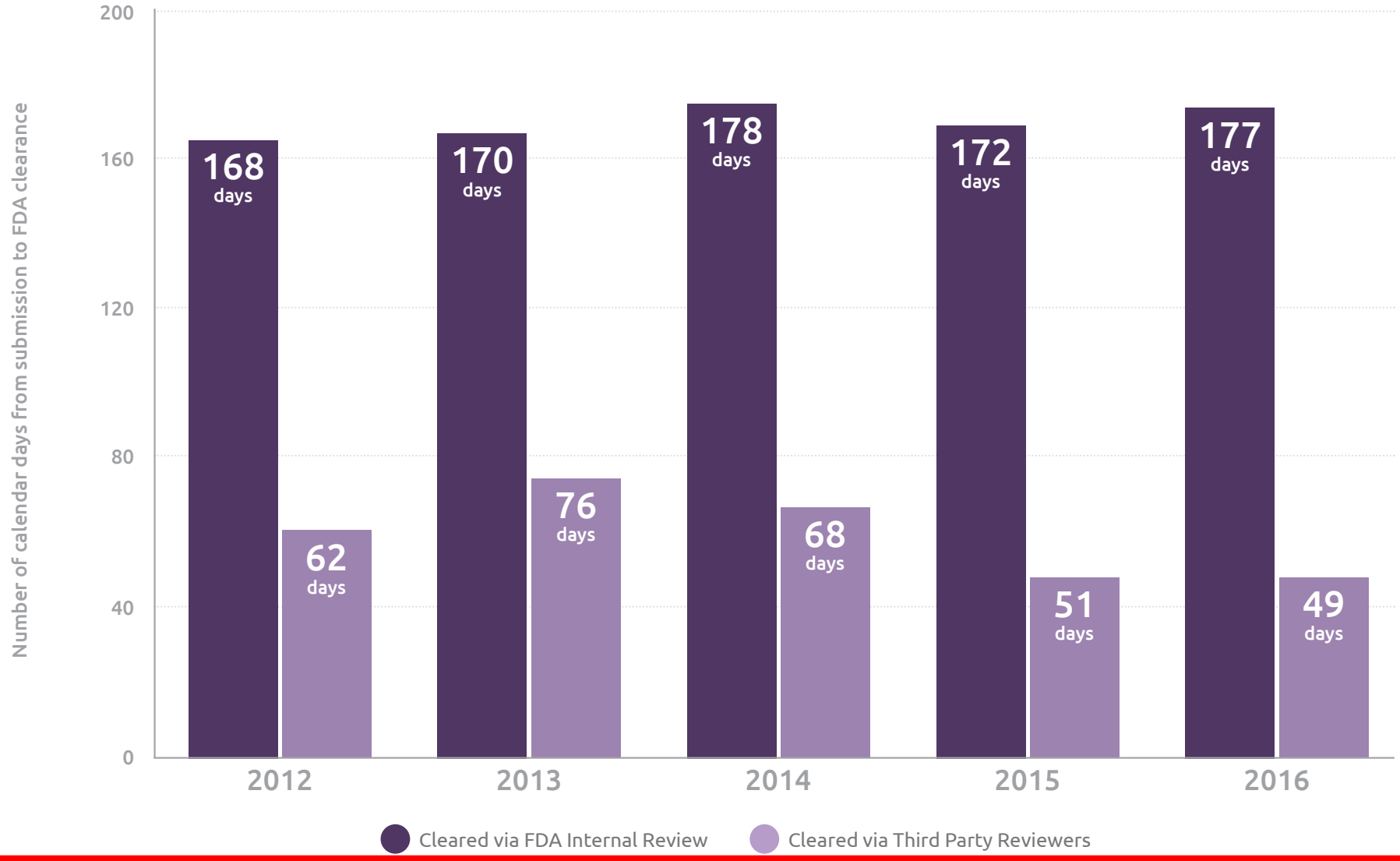
Number of traditional 510(k) submissions cleared by FDA internal reviewers over time

The 510(k) process started in mid-1976 and it took several years for the FDA to "ramp up." Starting around 1980s and continuing for another 10 years, volume increased markedly. Volume tapered off in the late 1990s and has since leveled off. However, the average time to obtain clearance continues a gradual upward march.



Calendar days from submission to FDA clearance – Traditional 510(k) only

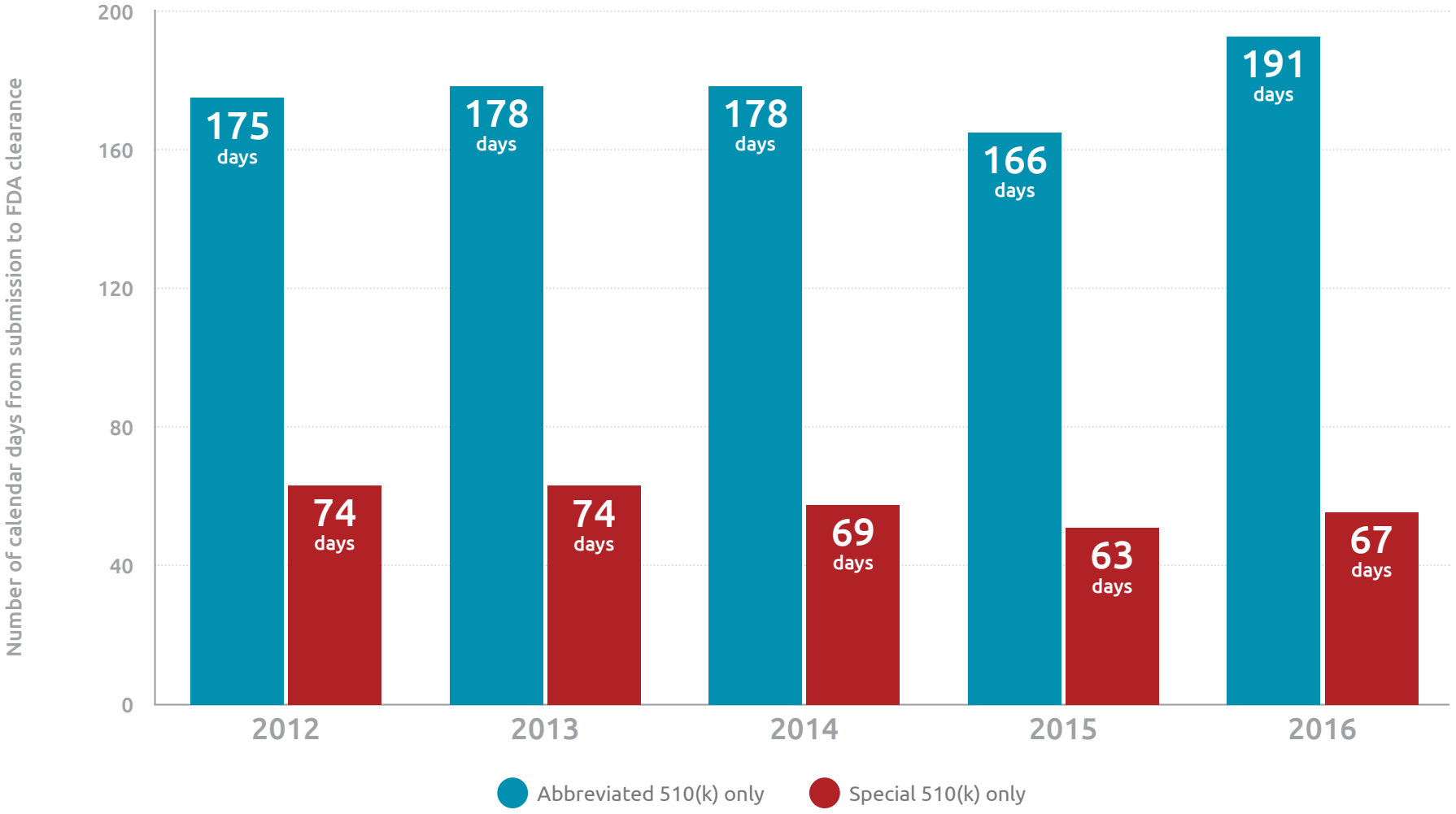
Many industry veterans long for a return to the days when you could get a traditional 510(k) cleared within 100 days. It still happens, but far less frequently than it did in the early 2000s. The FDA – like many other regulatory authorities - has become much more strict about clinical evidence and testing requirements, thus lengthening the overall path to clearance. Most companies can plan on waiting about six months to get the green light from FDA, although that varies by device (see page 8). Companies willing and able to utilize Third Party Reviewers can get to market about four months faster on average.



Calendar days from submission to FDA clearance – Abbreviated and Special 510(k) only

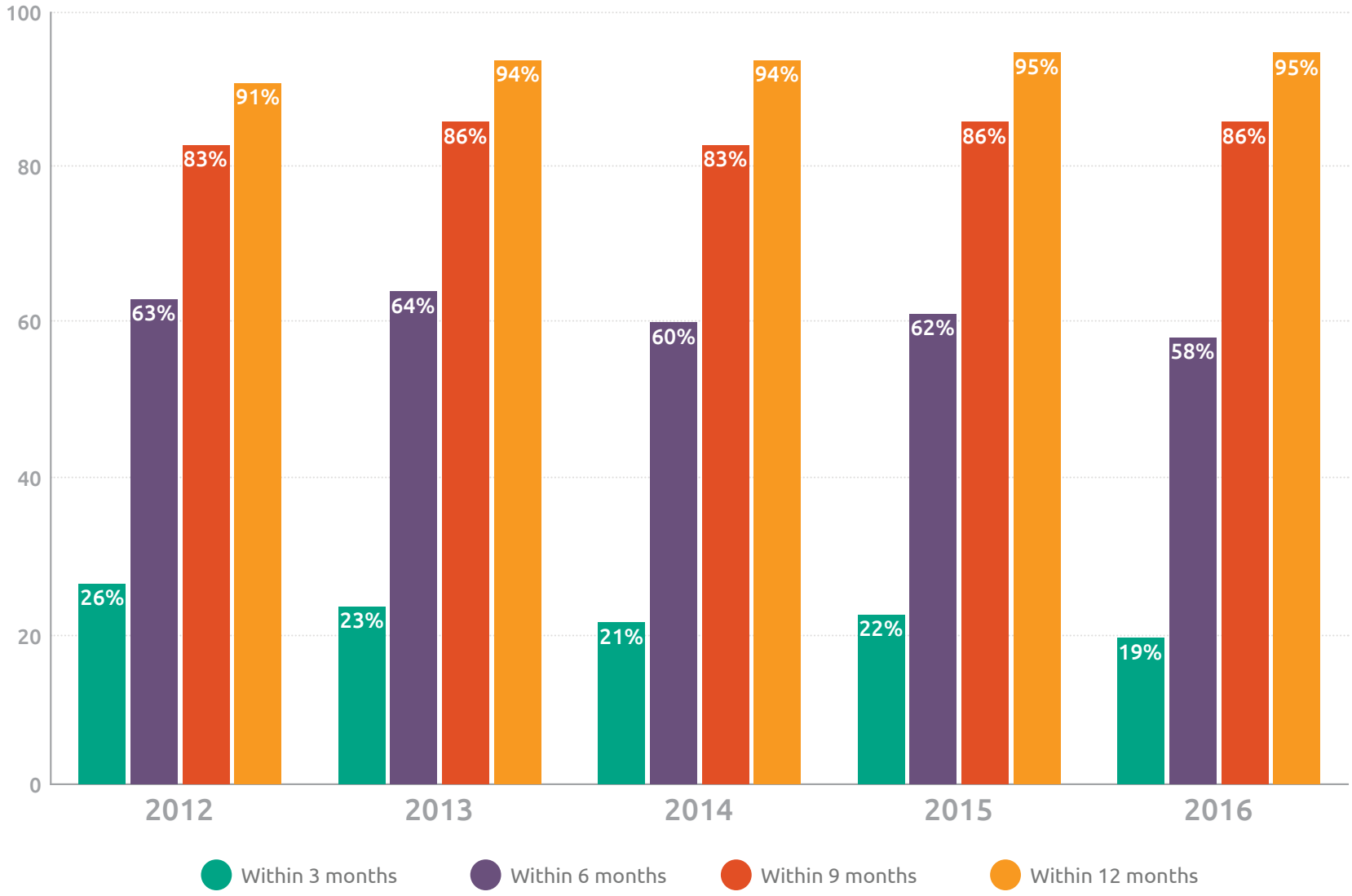
Despite their name, Abbreviated 510(k) submissions tend to take as long, or longer, to get cleared by the FDA. That probably explains why only 3% of all 510(k) submissions go through the "Abbreviated" process. Companies can choose to submit an abbreviated 510(k) when guidance documents exist, a special control has been established or the FDA has recognized a relevant consensus standard.

Special 510(k) submissions, on the other hand, are processed fairly quickly. The Special 510(k) is used when a modification has been made to a device. It allows the manufacturer to declare conformity with the Design Controls requirements of the Quality System Regulation (21 CFR Part 820) but not provide the supporting data.



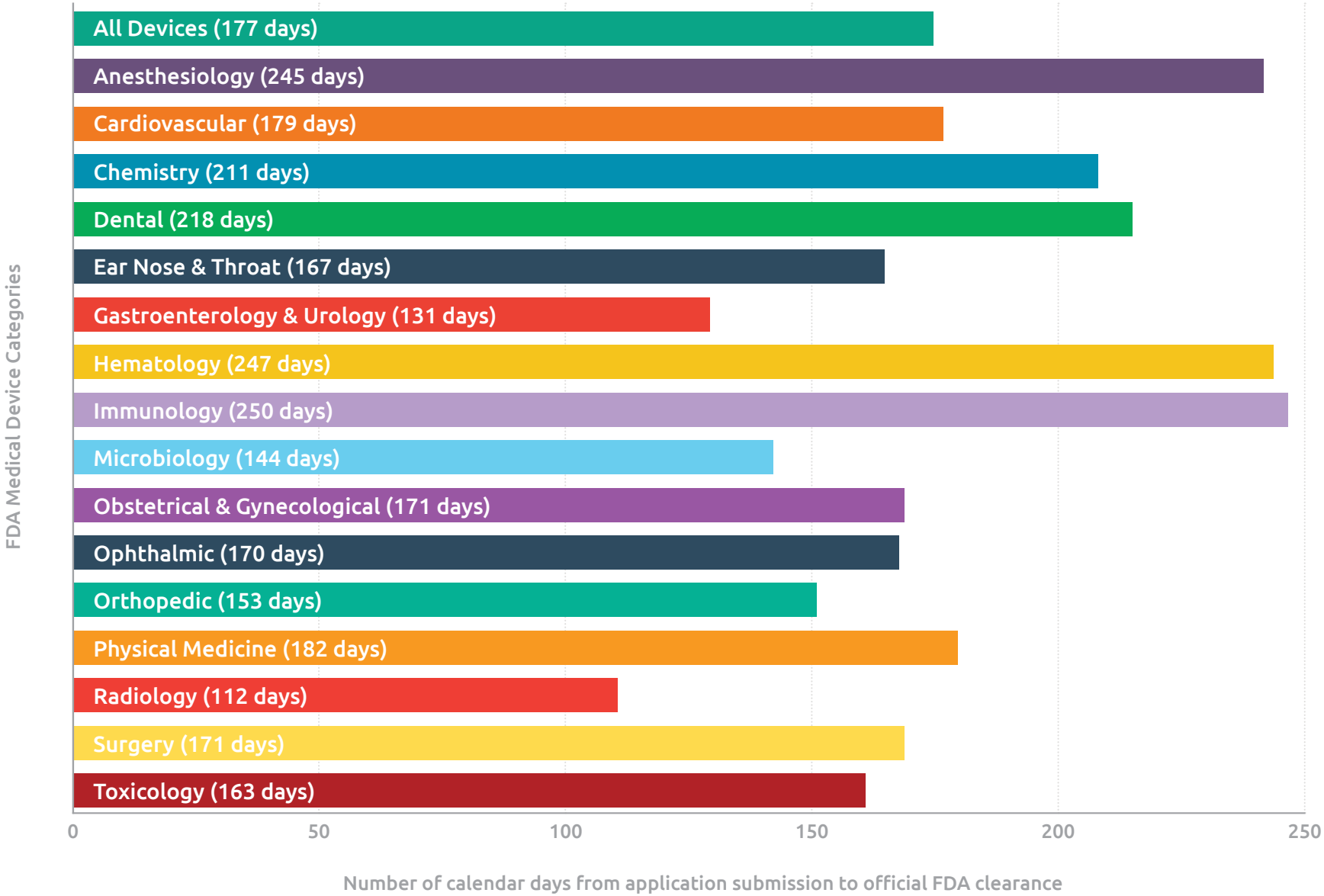
Percent of devices cleared within 3, 6, 9 and 12 months

As seen previously, the overall time to get a traditional 510(k) cleared has remained fairly steady over the last five years. Nonetheless, your chances of getting clearance within three months has diminished somewhat since 2012. Clearance times do vary significantly by device category. See page 8 for details.



Average calendar days from submission to clearance, by medical device type

As shown on page 5, companies waited 177 calendar days (about six months) on average for their device to get cleared by FDA during 2016. However, timeframes vary significantly by category of device. As might be expected, devices related to anesthesiology, immunology and hematology take considerably longer to get cleared whereas radiology devices tend to have a much shorter route to market.



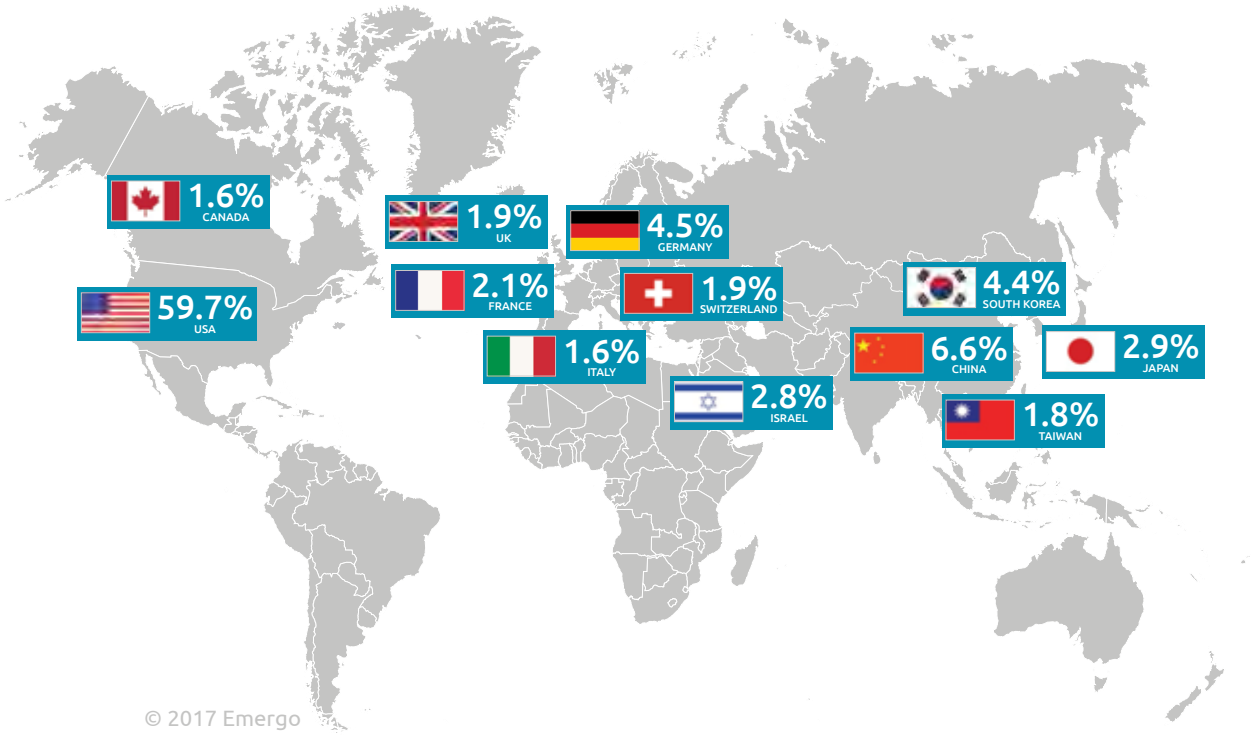
Huge increase in submissions from non-US companies

Starting in 2015, a significant shift started to occur in the number of non-US companies submitting 510(k) applications to the FDA. To be clear, the data should not be construed to mean that most 510(k) submissions are made by US companies. Many larger foreign medical device companies have US subsidiaries that submit applications on their behalf.

Nonetheless, the data shows that 510(k) submissions from Asian and European companies has nearly doubled in the last two years. Why? Some of the increase can be attributed to the strong US Dollar which makes imported medical devices cheaper for US buyers. The exchange rate really started to shift in September 2014, encouraging many European and Asian companies to enter the US market in 2015 and 2016 knowing they would be in a better position to compete with US companies. During the past two years, significant increases in the overall number of 510(k) submissions were seen from firms located in Germany, Italy, Switzerland, China, Japan and South Korea.

The increase in submissions from Chinese manufacturers has less to do with currency rates and more to do with the fact that they are becoming more sophisticated and export savvy. The upward trend has been steady for several years and Chinese device companies continue to introduce more devices to the US market than any other country.

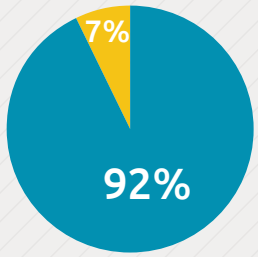
Share of all 510(k) submissions submitted by companies located in specific countries in 2016



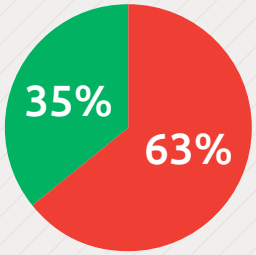
510(k) Clearances by Country of Origin			
Country	2014	2015	2016
Canada	1.0%	1.3%	1.6%
China	5.9%	7.0%	6.6%
France	1.0%	2.5%	2.1%
Germany	2.3%	3.7%	4.5%
Israel	1.4%	1.5%	2.8%
Italy	0.8%	1.5%	1.6%
Japan	0.8%	2.3%	2.9%
South Korea	1.1%	2.9%	4.4%
Switzerland	0.5%	1.6%	1.9%
Taiwan	1.3%	2.4%	1.8%
UK	1.4%	1.8%	1.9%
USA	78.1%	63.3%	59.7%

Fun FDA 510(k) facts

Devices that require a 510(k)



Percent of all FDA listed devices that go through 510(k) process



Number of devices cleared via FDA 510(k) process since 1976

142,000

Number of devices cleared via FDA each year, give or take 10%

3,000

40 Average calendar days time to get a 510(k) cleared in late 1970s and early 1980s

3,037 Longest period recorded (calendar days) to get a 510(k) cleared

Did You know?
All 510(k) submissions are assigned a "K number" – the letter K followed by six digits. The first two digits of the 510(k) number indicate the year it was submitted to FDA for review. The next four digits are sequential starting at 0 and indicate the order in which the submission was received during the year. The first 510(k) ever was submitted by Zimmer Inc. which holds K760001, submitted on May 26, 1976. Boston Scientific Scimed Inc. is the proud owner of K000001. No, it's not the first 510(k) ever, but it was the first one submitted in the new millennium on January 3, 2000! Many others were submitted that same day but theirs made it to the top of the pile.

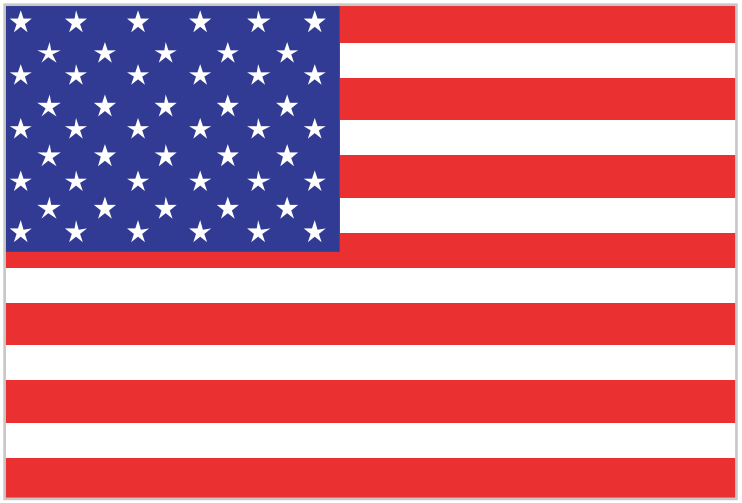
Learn more about the FDA 510(k) process

If you would like to learn more about how the 510(k) process works, or how Emergo can help, just follow the links provided below.

Preparing a US FDA Medical Device 510(k) Submission Learn More→

Introduction to US FDA Medical Device Regulatory Process Learn More→

US FDA Registration Process for Medical Devices Learn More→



US FDA Registration Process for Medical Devices Learn More→

United States

US

The regulatory process for medical devices

Using the FDA classification database, determine the classification of your device by researching "Predicate Devices" already registered in the US market.
Pay special attention to the three letter Product Code and seven digit Regulation Number associated with the predicate devices you identify.
If no predicate found, use 513(g) or De Novo process.

Class I	Class II	Class III
Implement Quality Management System (QMS) which meets FDA Quality System Regulation (QSR) found in 21 CFR Part 820. This is also commonly known as FDA Good Manufacturing Practice (GMP).		
	Innovative Class II, and all Class III, devices will likely require clinical studies. Get "Pre-Submission (Pre-Sub)" feedback from the FDA.	
	If clinical studies will be required, apply for an Investigational Device Exemption (IDE). Develop clinical trial protocol and conduct studies.*	
	Prepare and submit 510(k) premarket notification application. Pay 510(k) review fee to FDA.	Prepare* and submit Premarket Approval (PMA) application. Pay PMA submission fee to FDA.
		FDA conducts facility inspections of all major suppliers involved in the design and production of your device. All parties must be compliant with FDA QSR.
	FDA issues 510(k) clearance letter; posts online.	FDA issues PMA approval letter; posts online.
At this time, you must be in full compliance with QSRs. The FDA will not inspect Class I or II device manufacturers for compliance prior to device registration but does conduct random inspections and can issue a Form 483 for non-compliance.		
If you have no local presence in the US, appoint an FDA US Agent representative as a local point of contact with the FDA.		
List your device and register your company using FURLS system on the FDA website in accordance with 21 CFR Part 807; contract manufacturers and sterilizers must also register and list. Specify your appointed US Agent. Your FDA Establishment Registration and Listing must be renewed on a yearly basis		
You are now able to sell your device in the US. The FDA listing on their website will serve as your authorization to commercialize your device in the US. This authorization does not expire as long as certain types of changes are not made, e.g., design, intended use.		

* The process of supplying clinical study data in support of a PMA submission is far more complex than presented in this chart. This is an extremely simplified and high level view of the FDA requirements regarding clinical study data.

This is a simplified overview of the process. The FDA may choose to audit your submission and request more documents, which will add time to your approval.

5002-0914

United States

The regulatory process for medical devices

US

Device classification in USA	How long you should expect to wait after submission until approval is granted. (See note 1)	Validity period for device registrations. (See note 2)	Registration renewal should be started this far in advance. (See note 3)	Complexity of the registration process for this classification. (See note 4)	Overall cost of gaining regulatory approval. (See note 5)
CLASS I*	1 month	Does not expire	Not applicable	Simple – Complex	Low – High
CLASS II	3-6 months	Does not expire	Not applicable	Simple – Complex	Low – High
CLASS III**	18-30 months	Does not expire	Not applicable	Simple – Complex	Low – High

NOTE 1: The time frames shown above are typical for the majority of medical device submissions but assume that your device does not contain animal tissue, medicinal substances or employ entirely novel technology. Your length of approval will depend on the quality and completeness of your technical documentation and how much time you take to address additional information requests from authorities after submission. YOUR SUBMISSION(S) MAY TAKE MORE TIME THAN WHAT IS SHOWN ABOVE.

NOTE 2: Authorization to market your device does not expire as long as you do not make changes to the intended use, or changes to the device itself or its indications for use. However, your establishment registration (for your company) must be renewed annually, and the appropriate fees submitted. Failure to renew your annual establishment registration may result in you being prohibited from marketing your devices in the USA.

NOTE 3: The device registration does not expire, so no renewal is required. However, you must continue to pay your annual establishment registration fee for your company.

NOTE 4: Our rating of the complexity of the registration process is based on our experience and the opinion of nearly 1,000 QA/RA professionals worldwide who were asked to rate the difficulty of registering a device in each country in January 2014. The European CE Marking process is considered the mid-point to which all other markets are compared.

NOTE 5: Low = Less than US$5000; Midpoint = US$15000-$30000: High = More than US$50000. Overall cost includes registration application fees, product testing, in-country representation, submission preparation consulting and translation of registration documents but not IFU. Costs do not include cost of implementing, auditing, or updating a quality management system compliant with US FDA 21 CFR Part 820.

* Most Class I devices do not need to be cleared or approved for sale by the FDA but do need to be listed with the FDA using the FDA website. Once appropriate establishment registration fees are paid and verified, you will be able to complete the listing of your Class I device online.

** Devices which the FDA has not previously classified based on risk are automatically placed into Class III by the FDA, regardless of the level of risk they pose. Some lower risk devices without a predicate device may qualify for the “de novo” process which may result in a Class I or II designation by the FDA.

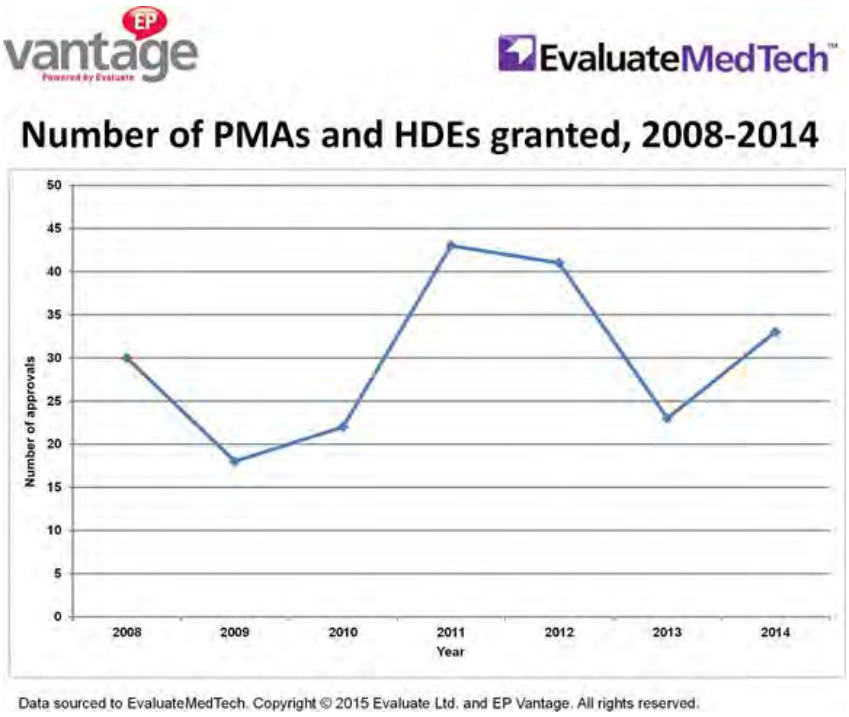
Export

FDA device approvals get faster still

Date January 27, 2015

Not quite as good as expected, but not too shabby. The FDA approved 33 innovative devices in 2014, a 43% increase on the number it greenlit the year before. When EP Vantage looked at the sector at the half-year point, we forecast 34 approvals by the year end, so this is very nearly as expected; however, the number is still down compared with 2011 and 2012 (see graph below).

The good news is that approval times are speeding up. Last year, it took an average of just 17.6 months to get a medical device through the FDA's most stringent regulatory pathway – a first-time premarket approval (PMA) – compared with nearly twice as long the year before. With the FDA's efforts to lighten the regulatory burden just beginning to take effect, this could get even faster in future.



The FDA has already signalled its willingness to speed up the approval process. Initiatives such as bringing in an expedited device approval pathway and streamlining the de novo approval process will soon bear fruit (The FDA's latest push to speed medtech approvals, August 28, 2014).

But neither of these are responsible for the change so far. The expedited route is not yet in force, and de novo approvals are not counted in this analysis. It seems that the FDA has simply made general efforts to hasten approvals.

Still, it should be noted that these sample sizes are small, and that the approval numbers and speed can fluctuate from year to year depending on the complexity of the products that happen to be submitted, and the quality of those submissions.

First-time PMAs by therapy area, 2013 and 2014

EvaluateMedTech classification - L1	First PMAs in 2013	Avg review time in 2013	First PMAs in 2014	Avg review time in 2014
Anesthesia & Respiratory	1	61.3	1	12.0
Blood	-	-	2	8.7
Cardiology	7	17.1	10	13.0
Diabetic care	1	15.7	1	19.0
Diagnostic imaging	1	16.8	1	13.0
Ear, nose & throat	-	-	1	9.5
General & plastic surgery	3	68.2	1	28.7
In vitro diagnostics	4	8.6	8	13.4
Neurology	1	40.5	-	-
Ophthalmics	-	-	1	11.0
Orthopaedics	2	30.0	3	48.0
Wound management	1	31.2	-	-
Total	21	-	29	-
Average	-	32.2	-	17.6

NB: this analysis does not include HDE approvals as not all data are yet available

Whatever the reasons, device companies are surely not complaining. At the half-year point, it took the agency an average of 18.4 months to grant 17 PMAs (FDA grants twice as many device approvals in half the time, July 25, 2014). Looking at the second half, only 12 devices gained PMAs, but they did so in an average of just 15 months.

One company that made a strong showing in the last six months is Medtronic, which as of today is the largest medtech company in the world. The approval of the IN.PACT Admiral drug-eluting balloon in atherosclerosis could in fact leave the company somewhat deflated; despite beating C. R. Bard's rival Lutonix device to the European market by two years, Medtronic's balloon was pipped to the US post when Lutonix was approved three months earlier than expected.

It is almost a surprise to see Myriad Genetics grace the table. For years the company sold its BRACAnalysis breast cancer gene assay in the US as a homebrew test, unregulated by the FDA, and enforced a monopoly by claiming to have patented the BRCA genes rather than the diagnostic.

A succession of legal defeats combined with forthcoming changes to the way the FDA will regulate diagnostics essentially forced the company to seek a PMA for BRACAnalysis as a companion diagnostic for AstraZeneca's ovarian cancer drug Lynparza (Astra's Lynparza becomes first Parp inhibitor, December 22, 2014). Achieving FDA approval is always a good move, but Myriad and its investors might feel somewhat disappointed.

Glut of HDEs

Looking at the FDA approvals in the last six months of 2014, perhaps the most interesting aspect is how few of them are traditional PMAs. Three of the 16 innovative devices approved in the second half carry BP codes, indicating that they were approved by the FDA's Center for Biologics Evaluation and Research rather than its Center for Devices and Radiological Health, which grants approvals with P codes.

BP code approvals are still PMAs, however. Arguably more interesting is the sudden glut of humanitarian device exemptions (HDEs), a different kind of approval for innovative devices. These once-rare designations are the rough equivalent of orphan drug approvals in biopharma, and permit a slightly lower burden of proof when it comes to efficacy.

The FDA granted four HDEs in 2014, all in the second half of the year – indeed some are so recent that the agency has not yet released full data on them. Perhaps more HDE applications are being submitted, and the medtech industry beginning to target rare diseases with the same enthusiasm as the biopharma sector. Or perhaps the uptick in HDEs is another result of a more relaxed attitude at the FDA.

First-time PMAs and HDEs granted by the FDA in the second half of 2014

Device Name	EvaluateMedTech Device Classification - L1	EvaluateMedTech Device Classification - L3	Company	Number (510(k)/PMA)	Decision Date	FDA Review Time (Months)
Prestige LP cervical disc	Orthopedics	Artificial Discs	Medtronic	P090029	July 24, 2014	55.1
Low-profile visualized intraluminal support device (Luvs and Luvs Jr)	Neurology	Neurovascular Devices	Terumo	H130005	July 25, 2014	8.9
Cologuard	In Vitro Diagnostics	Oncology Molecular Diagnostics	EXACT Sciences	P130017	August 11, 2014	14.1
Xvivo Perfusion System	Anesthesia & Respiratory	Other Respiratory Therapeutic Devices	Xvivo Perfusion	H120003	August 12, 2014	25.3
Pleximinune	In Vitro Diagnostics	Other Clinical Chemistry	Sirrdor Life Sciences	H130004	August 26, 2014	12.4
SenoClaire	Diagnostic Imaging	Other Computed Tomography	General Electric	P130020	August 26, 2014	13.0
Lutonix	Cardiology	Drug-Eluting Balloons	C. R. Bard	P130024	October 9, 2014	10.5
Geenius HIV 1/2 Supplemental Assay	In Vitro Diagnostics	Viral Immunoassays	Bio-Rad Laboratories	BP140120	October 24, 2014	0.9
Tacticath	Cardiology	Cardiac Ablation Catheters	St. Jude Medical	P130026	October 24, 2014	10.8
Ideal implant	General & Plastic Surgery	Breast Prostheses	Valeant Pharmaceuticals International	P120011	November 14, 2014	28.7
Animas Vibe	Diabetic Care	Insulin Pumps	Johnson & Johnson	P130007	November 25, 2014	19.0
Barostim neo Legacy	Neurology	Unclassified	CVRx	H130007	December 12, 2014	Unknown
Intercept blood system for plasma	Blood	Unclassified	Cerus	BP130076	December 16, 2014	11.8
Intercept blood system for platelets	Blood	Unclassified	Cerus	BP140143	December 18, 2014	5.6
BRACAnalysis CDX	In Vitro Diagnostics	Oncology Molecular Diagnostics	Myriad Genetics	P140020	December 19, 2014	2.8
IN PACT Admiral	Cardiology	Drug-Eluting Balloons	Medtronic	P140010	December 30, 2014	7.1

To contact the writer of this story email Elizabeth Cairns in London at elizabethc@epvantage.com or follow @LizEPVantage on Twitter

Report: Average 510(k) Review Time of 138 Days Remains Close to Record Highs

Posted 19 February 2013

By Alexander Gaffney, RF News Editor (/SearchRegFocus.aspx?name=Alexander Gaffney)

A recent report (http://www.emergogroup.com/research/download-fda-510k-review-times-research) published by consulting company Emergo Group shows that review times for 510(k) submissions improved slightly in 2011, but remains close to the record highs seen in 2010 that have upset (http://www.raps.org/focus-online/news/news-article-view/article/1065/survey-fda-510k-submissions-garner-most-concern-among-device-professionals.aspx) many in industry.

Emergo's report, *An Analysis of US FDA 510(k) submissions received between 2006 and 2011*, tracks statistics associated with 510(k) premarket notification submissions. Under FDA regulations, companies intending to market a device that is substantially equivalent to an already-approved predicate device must notify the agency at least 90 days in advance of marketing the product.

But just proving substantial equivalence can be difficult, and regulators have been seen as wary in recent years to approve some products in the wake of notable lapses in safety. Metal-on metal hip implants, defibrillator leads, heart valve rings and vaginal mesh products have all been associated with (http://www.propublica.org/special/four-medical-implants-that-escaped-fda-scrutiny) serious safety concerns, and all were cleared by FDA via the 510(k) pathway.

As those concerns have mounted, the number of 510(k) submissions approved by FDA each year has plummeted compared to the number of products cleared just five years ago. In 2006, FDA managed to clear 3,325 510(k) submissions, the report notes. The year after, just 3,068–a 7.7% decrease in just a single year.

Since then, that decrease has become the new baseline for approvals. In 2008, FDA cleared 3,134 devices; 3,104 in 2009; 2929 in 2010; and 3,055 in 2011.

2011's clearance number might stand to rise between 3-5% once the final batch of 510(k) submissions are cleared by FDA in early 2013, Emergo noted.

Average Review Times-Cause for Concern?

Many companies, however, haven't been as concerned about the number of 510(k) submissions cleared by FDA as the time it takes, on average, for them to receive a clearance decision. Emergo's data shows this concern is well-founded, with average clearance times increasing in five of the last six years.

The average clearance in 2006 took 97 days, the report shows. By 2010, that time has increased by 50% to 146 days on average. While 2011 saw a slight improvement (138 days on average), that could be cold comfort for an industry that has long complained that delays are jeopardizing its returns on investment and ability to innovate.

Not all devices, it should be noted, are created equal. A radiology device takes 79 days on average to clear-by far the shortest time of all devices assessed by Emergo. The next fastest device category was cardiovascular devices, which were cleared in 105 days on average. At the other end of this spectrum were immunology devices, which took 201 days on average to clear, and pathology devices, which ranked worst at 204 days to clear on average.

One reason behind those averages might be economies of scale. Devices that constituted the highest percentage of 510(k) submissions tended to have the smallest average number of calendar days from submission to clearance. Orthopedic devices, which constituted 15.8% of all devices, took just 115 days on average to approve. Clinical toxicology devices, which constituted 1.3% of all 510(k) submissions, took third-longest at 185 days on average.

The top 20 most common medical devices all took below 120 calendar days on average to obtain clearance, the report notes.

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Regulatory Exchange: Latest Updates From the Community

RE: Packaging tablets for a biostudy (https://connect.raps.org/communities/community-home/digestviewer/viewthread/?MessageKey=94426dc0-8237-44a0-bd6f-dad6d7fd0048&CommunityKey=5af348a7-851e-4594-b467-d4d0983b6d89&tab=digestviewer#bm94426dc0-8237-44a0-bd6f-dad6d7fd0048)

The bio-study samples needs to be representative of that particular batch. It can be sampled randomly by sponsor from all the packaged bottles and send it to testing laboratory.

For exhibit...

RE: HIPAA and Complaints (https://connect.raps.org/communities/community-home/digestviewer/viewthread/?MessageKey=41c33478-32e9-4ac9-a021-963aebf70c49&CommunityKey=5af348a7-851e-4594-b467-d4d0983b6d89&tab=digestviewer#bm41c33478-32e9-4ac9-a021-963aebf70c49)

Thanks, Mark. I'll message you privately later for more information.

Stephanie Morris
United Consortium
Valencia CA
United States

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RE: Manuals and IFUs: Online vs paper form (https://connect.raps.org/communities/community-home/digestviewer/viewthread/?MessageKey=17fb1ad1-fdf8-4d1d-bb2f-6d2bd53b921e&CommunityKey=5af348a7-851e-4594-b467-d4d0983b6d89&tab=digestviewer#bm17fb1ad1-fdf8-4d1d-bb2f-6d2bd53b921e)

Elizabeth,

Great question. The EU does not recognize Kegel exercisers as medical devices, while the FDA does. As such, there are different indications for the different markets. I was cha...

RE: Manuals and IFUs: Online vs paper form (https://connect.raps.org/communities/community-home/digestviewer/viewthread/?MessageKey=326570d5-546a-43e5-99b4-5bcb0867025e&CommunityKey=5af348a7-851e-4594-b467-d4d0983b6d89&tab=digestviewer#bm326570d5-546a-43e5-99b4-5bcb0867025e)

Thank you so much for responding. The eIFU the company is proposing will be a consolidated version inclusive of 4 device types, only one of which is a 510(k) "required" device. Essentially, what the...

EXHIBIT B

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 16 Footnote 2

Premarket Notification 510(k)

- Introduction
- What is Substantial Equivalence
- Who is Required to Submit a 510(k)
- When a 510(k) is Required
- When a 510(k) is not Required
- Preamendment Devices
- Third Party Review Program

Introduction

Each person who wants to market in the U.S., a Class I, II, and III device intended for human use, for which a Premarket Approval (PMA) is not required, must submit a 510 (k) to FDA unless the device is exempt from 510(k) requirements of the Federal Food, Drug, and Cosmetic Act (the Act) and does not exceed the limitations of exemptions in .9 of the device classification regulation chapters (e.g., 21 CFR 862.9, 21 CFR 864.9). There is no 510(k) form, however, **21 CFR 807 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807&showFR=1&subpartNode=21:8.0.1.1.5.5)** Subpart E describes requirements for a 510(k) submission. Before marketing a device, each submitter must receive an order, in the form of a letter, from FDA which finds the device to be substantially equivalent (SE) and states that the device can be marketed in the U.S. This order "clears" the device for commercial distribution.

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that was legally marketed prior to May 28, 1976 (preamendments device), for which a PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process. The legally marketed device(s) to which equivalence is drawn is commonly known as the "predicate." Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device may be used as a predicate. Legally marketed also means that the predicate cannot be one that is in violation of the Act.

Until the submitter receives an order declaring a device SE, the submitter may not proceed to market the device. Once the device is determined to be SE, it can then be marketed in the U.S. The SE determination is usually made within 90 days and is made based on the information submitted by the submitter.

Please note that FDA does not perform 510(k) pre-clearance facility inspections. The submitter may market the device immediately after 510(k) clearance is granted. The manufacturer should be prepared for an FDA quality system (21 CFR 820) inspection at any time after 510(k) clearance.

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What is Substantial Equivalence

A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate.

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate;
  or
- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA;
  - does not raise new questions of safety and effectiveness; **and**
  - demonstrates that the device is at least as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.

A device may not be marketed in the U.S. until the submitter receives a letter declaring the device substantially equivalent. If FDA determines that a device is **not** substantially equivalent, the applicant may:

- resubmit another 510(k) with new data,
- request a Class I or II designation through the **de novo (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm462775.htm)** process
- file a **reclassification petition (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=860&showFR=1&subpartNode=21:8.0.1.1.15.3)**, or
- submit a premarket approval application (PMA).

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Who is Required to Submit a 510(k)

The Act and the 510(k) regulation (21 CFR 807) do not specify who must apply for a 510(k). Instead, they specify which actions, such as introducing a device to the U.S. market, require a 510(k) submission.

The following four categories of parties must submit a 510(k) to the FDA:

1. Domestic manufacturers introducing a device to the U.S. market;

   Finished device manufacturers must submit a 510(k) if they manufacture a device according to their own specifications and market it in the U.S. Accessories to finished devices that are sold to the end user are also considered finished devices. However, manufacturers of device components are not required to submit a 510(k) unless such components are promoted for sale to an end user as replacement parts. Contract manufacturers, those firms that manufacture devices under contract according to someone else' s specifications, are not required to submit a 510(k).
2. Specification developers introducing a device to the U.S. market;

   A specification developer develops the specifications for a finished device, but has the device manufactured under contract by another firm or entity. The specification developer submits the 510(k), not the contract manufacturer.
3. Repackers or relabelers who make labeling changes or whose operations significantly affect the device.

   Repackagers or relabelers may be required to submit a 510(k) if they significantly change the labeling or otherwise affect any condition of the device. Significant labeling changes may include modification of manuals, such as adding a new intended use, deleting or adding warnings, contraindications, etc. Operations,

such as sterilization, could alter the condition of the device. However, most repackagers or relabelers are not required to submit a 510(k).

4. Foreign manufacturers/exporters or U.S. representatives of foreign manufacturers/exporters introducing a device to the U.S. market.

Please note that all manufacturers (including specification developers) of Class II and III devices and select Class I devices are required to follow design controls (21 CFR 820.30) during the development of their device. The holder of a 510(k) must have design control documentation available for FDA review during a site inspection. In addition, any changes to the device specifications or manufacturing processes must be made in accordance with the Quality System regulation (21 CFR 820) and may be subject to a new 510(k). Please see our guidance, "**Deciding When to Submit a 510(k) for a Change to an Existing Device (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm)**."

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When a 510(k) is Required

A 510(k) is required when:

1. Introducing a device into commercial distribution (marketing) for the first time. After May 28, 1976 (effective date of the Medical Device Amendments to the Act), anyone who wants to sell a device in the U.S. is required to make a 510(k) submission at least 90 days prior to offering the device for sale, even though it may have been under development or clinical investigation before that date. If your device was not marketed by your firm before May 28, 1976, a 510(k) is required.
2. You propose a different intended use for a device which you already have in commercial distribution. The 510(k) regulation (**21 CFR 807 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807&showFR=1&subpartNode=21:8.0.1.1.5.5)**) specifically requires a 510(k) submission for a major change or modification in intended use. Most, if not all changes in intended use will require a 510(k). Please note that prescription use to over the counter use is a major change in intended use and requires the submission of a new 510(k).
3. There is a change or modification of a legally marketed device and that change could significantly affect its safety or effectiveness. The burden is on the 510(k) holder to decide whether or not a modification could significantly affect safety or effectiveness of the device. Any modifications must be made in accordance with the Quality System regulation, 21 CFR 820, and recorded in the device master record and change control records. It is recommended that the justification for submitting or not submitting a new 510(k) be recorded in the change control records.

   A new 510(k) submission is required for changes or modifications to an existing device, where the modifications could significantly affect the safety or effectiveness of the device or the device is to be marketed for a new or different indication for use. See **Is a new 510(k) required for a modification to the device? (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134575.htm)** for additional information.

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When a 510(k) is Not Required

The following are examples of when a 510(k) is not required.

1. You sell unfinished devices to another firm for further processing or sell components to be used in the assembling of devices by other firms. However, if your components are to be sold directly to end users as replacement parts, a 510 (k) is required.

2. Your device is not being marketed or commercially distributed. You do not need a 510(k) to develop, evaluate, or test a device. This includes clinical evaluation. Please note that if you perform clinical trials with your device, you are subject to the **Investigational Device Exemption (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm)** (IDE) regulation (21 CFR 812).
3. You distribute another firm's domestically manufactured device. You may place a label on the device, "Distributed by ABC Firm" or "Manufactured for ABC Firm," (**21 CFR 801.1 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=801.1)**) and sell it to end users without submission of a 510(k).
4. In most cases, if you are a repackager or a relabeler you are not required to submit a 510(k) if the existing labeling or condition of the device is not significantly changed. The labeling should be consistent with the labeling submitted in the 510(k) with the same indications for use and warnings and contraindications.
5. Your device was legally in commercial distribution before May 28, 1976 and you have documentation to prove this. These devices are "grandfathered" and have **Preamendment Status (/MedicalDevices/DeviceRegulationandGuidance/MedicalDeviceQualityandCompliance/ucm379552.htm)**. You do not have to submit a 510(k) unless the device has been significantly modified or there has been a change in its intended use.
6. The device is made outside the U.S. and you are an importer of the foreign made medical device. A 510(k) is not required if a 510(k) has been submitted by the foreign manufacturer and received marketing clearance. Once the foreign manufacturer has received 510(k) clearance for the device, the foreign manufacturer may export his device to any U.S. importer.
7. Your device is exempted from 510(k) by regulation (21 CFR 862-892). That is, certain Class I or II devices can be marketed for the first time without having to submit a 510(k). A list of the Class I and II exempted devices can be found on **Medical Device Exemptions 510(k) and GMP Requirements (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm)**. However, if the device exceeds the limitations of exemptions in .9 of the device classification regulation chapters (e.g., 21 CFR 862.9, 21 CFR 864.9), such as the device has a new intended use or operates using a different fundamental scientific technology than a legally marketed device in that generic type of device, or the device is a reprocessed single-use device, then a 510(k) must be submitted to market the new device.

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Preamendment Devices

The term "preamendments device" refers to devices legally marketed in the U.S. by a firm before May 28, 1976 **and** which have not been:

- significantly changed or modified since then; **and**
- for which a regulation requiring a PMA application has not been published by FDA.

Devices meeting the above criteria are referred to as "grandfathered" devices and do not require a 510(k). The device must have the same intended use as that marketed before May 28, 1976. If the device is labeled for a new intended use, then the device is considered a new device and a 510(k) must be submitted to FDA for marketing clearance.

Please note that you must be the **owner** of the device on the market before May 28, 1976, for the device to be grandfathered. If your device is similar to a grandfathered device and marketed **after** May 28, 1976, then your device does NOT meet the requirements of being grandfathered and you must submit a 510(k). In order for a firm to claim that it has a preamendments device, it must demonstrate that its device was labeled, promoted, and distributed in interstate commerce for a specific intended use

and that intended use has not changed. See **Preamendment Status (/MedicalDevices/DeviceRegulationandGuidance/MedicalDeviceQualityandCompliance/ucm379552.htm)** for information on documentation requirements.

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Third Party Review Program

The Center for Devices and Radiological Health (CDRH) has implemented a Third Party Review Program. This program provides an option to manufacturers of certain devices of submitting their 510(k) to private parties (Recognized Third Parties) identified by FDA for review instead of submitting directly to CDRH. For more information on the program, eligible devices and a list of Recognized Third Parties go to **Third Party Review Program Information (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ThirdParyReview/default.htm)** page.

Top

References

- **CDRH Learn Module: 510(k) Program (http://fda.yorkcast.com/webcast/Play/d91af554691c4260b5eca0b2a28e636b1d) (/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)**
- **510(k) Frequently Asked Questions (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142654.htm)**
- **New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080195.htm)**
- **510(k) Decision-Making Flowchart (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf#page=30)**
- **The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] - Guidance for Industry and Food and Drug Administration Staff (PDF - 844KB) (/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf)**
- **Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm)**

Additional Information

- **510(k) Clearances (/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm)**

Contact FDA

1 (800) 638-2041
(301) 796-7100
DICE@fda.hhs.gov (mailto:DICE@fda.hhs.gov)

Information-Medical Devices / Radiation Products
Division of Industry and Consumer Education (http://www.fda.gov/dice)
CDRH-Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

More in Premarket Notification (510k) (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

510(k) Submission Process (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

510(k) Forms
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

510(k) Submission Methods
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

How To Prepare A Special 510(k)
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

How to Find and Effectively Use Predicate Devices
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How to Prepare a Traditional 510(k)
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How to Prepare an Abbreviated 510(k)
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Is a new 510(k) required for a modification to the device?
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Premarket Notification [510(k)] Review Fees
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

Special Considerations
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotificatic

EXHIBIT C

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 17 Footnote 3

REPORT BRIEF JULY 2011

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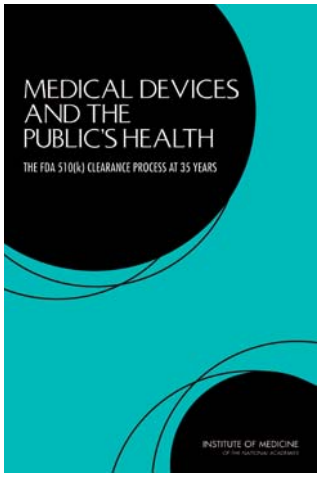
Medical Devices and the Public's Health

The FDA 510(k) Clearance Process at 35 Years



Medical devices play a critical role in the health care of Americans. They can range from simple tools, such as tongue depressors and bandages, to complex or life-saving equipment, such as pacemakers, magnetic resonance imaging machines, and heart–lung machines. Devices are used in healthcare facilities—such as hospitals, physicians' offices, and nursing homes—and at home.

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires a "reasonable assurance of safety and effectiveness" before a device can be marketed. The U.S. Food and Drug Administration (FDA) is responsible for enforcing this requirement. Devices that are deemed to have a moderate risk to patients generally cannot go on the market until they are cleared through the 510(k) process, named for Section 510(k) of the FFDCA. Devices that are subject to the 510(k) process include such devices as blood pressure cuffs as well as some types of contact lenses and pacemakers. The FDA received about 4,000 510(k) submissions in 2009.

Devices that are deemed to have a moderate risk to patients generally cannot go on the market until they are cleared through the 510(k) process, named for Section 510(k) of the FFDCA.

Some policymakers and patients have expressed concern about the ability of the 510(k) process to ensure that medical devices on the market are safe and effective. Other policymakers and patients, as well as the medical-device industry, have asserted that the process has become too burdensome and time-consuming and that it is delaying important new medical devices from entering the market.

The FDA turned to the Institute of Medicine (IOM), which appointed a committee to review the 510(k) process and answer two questions:

- Does the current 510(k) process protect patients optimally and promote innovation in support of public health?

- If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) process optimally?

The Legislative Framework of the 510(k) Process

Regulation of medical devices began in 1938 and reflected the relatively simple devices on the market at that time. By the 1970s, the original regulatory system no longer was adequate or flexible enough to deal with the growing array of device types and increasing sophistication of new devices. Sporadic public-health disasters associated with a few devices generated substantial public concern. Consequently, Congress passed the *Medical Device Amendments of 1976*, which established the framework for the current regulatory system, including the 510(k) process. Then, in 1990 and 1997, Congress passed sets of substantial changes to the 1976 statute. These three enactments serve as the basis of the legislative framework for the 510(k) process.

The law states that a moderate-risk device that is *substantially equivalent*, or similar, to any previously 510(k)-cleared device or any device that was on the market when the Medical Device Amendments were enacted—referred to as a *predicate device*—can be cleared for marketing with some exceptions. When the FDA assesses the substantial equivalence of a device, it generally does not require evidence of safety or effectiveness; and when a device is found to be substantially equivalent to a predicate device, the new device is assumed to be as safe and effective as the predicate because of its similarity. Devices that were on the market before the Medical Device Amendments were never systematically assessed for safety and effectiveness—but they are being used as predicate devices. This leads the committee to find that 510(k) clearance is not a determination that the cleared device is safe or effective. The committee concludes that the 510(k) process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate-risk devices and, furthermore, that it cannot be transformed into one.

The committee is not suggesting that all, many, or even any medical devices cleared through the 510(k) process and currently on the market are unsafe or ineffective. The continual use of many of these devices in clinical practice provides reason for a level of confidence in their safety and effectiveness.

Innovation and the 510(k) Process

The committee defines innovation as something that improves the quality of, efficiency of, or access to health care. The 510(k) process does not require a moderate-risk device to be innovative, nor does it reward innovation. However, the 510(k) process can facilitate innovation by making new devices available to consumers in a timely manner.

It is unclear—and the committee concludes that it is indeterminable, given current information—whether the 510(k) process over the last 35 years has had a positive or negative effect on innovation. To answer this question, the FDA should commission an assessment to determine this effect.

The Medical Device Regulatory System

The 510(k) process does not operate in isolation. Premarket review, including the 510(k) process, and postmarket oversight—from product labeling regulations to the reporting of adverse events associated with use of a device—make up a comprehensive medical device regulatory system. All the components of the system need to be functioning well in order to provide a reasonable assurance of the safety and effectiveness of medical devices.

The committee concludes that the 510(k) process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate-risk devices and, furthermore, that it cannot be transformed into one.

No premarket regulatory system for medical devices can guarantee that all new medical devices will be completely safe and effective when they reach the market. Robust postmarketing surveillance is essential. The committee identified substantial problems in the current postmarketing surveillance of devices. The FDA should develop and implement a comprehensive strategy to collect, analyze, and act on medical device aftermarket performance information.

It is important for the FDA to use postmarket enforcement tools, such as seizing or banning a device, when necessary. The FDA has stated that there are limitations to the use of these tools but has not identified the limitations. The agency should review its postmarket regulatory powers to identify these limitations and address them.

The committee recommends that the FDA develop and implement a program of continuous quality improvement to increase predictability, transparency, and consistency in all regulatory decisions for devices and to address emerging issues that affect decision making.

Moving Forward

The committee finds that the current 510(k) process is flawed based on its legislative foundation. Rather than continuing to modify the 35-year-old 510(k) process, the committee concludes that the FDA's finite resources would be better invested in developing an integrated premarket and postmarket regulatory framework that provides a reasonable assurance of safety and effectiveness throughout the device life cycle. This new framework should:

- be based on sound science;
- be clear, predictable, straightforward, and fair;
- be self-sustaining and self-improving;
- facilitate innovation that improves public health by making medical devices available in a timely manner and ensuring their safety and effectiveness throughout their lifecycle;
- use relevant and appropriate regulatory authorities and standards throughout the life cycle of devices to ensure safety and effectiveness; and
- be risk-based.

Current information is not adequate to design a new framework, and the FDA should begin to obtain the needed information. Once adequate information is available to design an appropriate medical-device regulatory framework, Congress should enact legislation to do so. A new regulatory framework will benefit everyone—patients, healthcare providers, the medical device industry, payers, and the FDA.

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EXHIBIT D

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 21 Footnote 4

OIVD Workshop
Premarket Notification (510(k))

April 22, 2003
Parklawn Building
Rockville, MD

Presented by
Marjorie Shulman
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health
(301) 594-1190 x 144

What is a 510(k)?

- Premarket Notification
- Section 510(k) of F,D, & C Act
- 21 CFR 807 Subpart E
- Marketing Clearance Application
- Allows FDA to Determine Substantial Equivalence (SE)

What a 510(k) Is Not

- A form
- Establishment Registration (FDA-2891)
- Device Listing (FDA-2892)
- Premarket Approval (PMA)
- Product Development Protocol (PDP)

A Device is Substantially Equivalent (SE) if:

- In Comparison to a legally marketed device, it:
- Has the same intended use, and
- Has the same technological characteristics as the predicate device, or:

SE (cont.)

- Has the same intended use, and
- Has different technological characteristics and the information in the 510(k):
- Does not raise new questions of safety and effectiveness, and
- Demonstrates it is as safe and effective as the predicate

May 28, 1976

- PREAMENDMENT DEVICE:
  Exempted (with Conditions)
  from Marketing Clearance
- POSTAMENDMENT DEVICE:
  Requires Marketing Clearance

Establish Equivalence to:

- A legally marketed device that does not require a PMA, i.e., a:
  - Preamendments device, or
  - A device found by FDA to be Substantially Equivalent (SE), or
  - A reclassified device

FDA finds the device Substantially Equivalent?

- NO:
  - PMA Application
    - or
  - PDP Application
    - or
  - DeNovo Application
- YES:
  - To Market

510(k) Submission Required When:

- Introducing a device to the market for the first time
- Change in intended use for a marketed device
- Making significant modification to a marketed device

Modifications -

- Changes in Intended Use
- Modifications that significantly enhance (or decrease) Safety or Effectiveness, e.g.
  - -change in design, materials, chemical composition, energy source, or manufacturing process
- Guidance: "Deciding When to Submit a 510(k) for Change to an Existing Device" (1/10/97)

Who Must Submit a 510(k)

- Manufacturers
- Specifications Developers
- Repackagers who change device or its labeling
- Relabelers who change the labeling, e.g., instructions for use

Who is Not Required to Submit a 510(k)

- Private Label Distributor who only adds company name and wording such as:
  - "Distributed by _____" or
  - "Manufactured for _____"

Not Required to Submit (cont.)

- Repackager who does not alter labeling
- Distributor or Importer who furthers marketing of the device and does not alter labeling or change device

Devices Exempt from 510(k)

- Unfinished Device
- Class I and II devices exempt by statute or regulation
- Finished device not sold in U.S.
- Device covered under another 510(k), i.e, private labeled device
- Preamendment device
- Custom Device

510(k) Content and Format

- 21 CFR 807.87 and 807.90
- Device Advice
- Device Specific Guidance
- 510(k) Refuse to Accept Checklist

510(k) Format

- Cover Letter or Cover Sheet
- User Fee Payment ID Number
- Table of Contents
- 510(k) Checklist
- Correct Pagination
- Required Information
- 1.5” left margin, unbound

Information Requested in 510(k) (21 CFR 807.87)

- Submitter's name, address, phone/fax #, contact person, rep./consultant name, establishment registration number
- Device Classification Name, CFR number, device class, procode
- Common/usual name and trade/proprietary name and model numbers

Information Requested (cont.) (21 CFR 807.87)

- Identification of marketed device(s) to which equivalence is claimed
- Compliance with section 514 Special Controls
- Proposed labels, labeling, and advertising

Information Requested (cont.) (21 CFR 807.87)

- Photographs, engineering drawings
- Substantially equivalent statement and comparison with predicate
- Statement of similarities and/or differences with predicate device
- Data for changes for modified devices

Information Requested (cont.) (21 CFR 807.87)

- 510(k) MUST include either:

510(k) Statement		510(k) Summary
Applicant gives 510(k) info to requesters within 30 days	or	FDA provides the summary to requesters via FOI process & Internet

*Content and Format (21 CFR 807.92 & 807.93)

Information Requested (cont.) (21 CFR 807.87)

- Class III 510(k) must include:
  - Certification and literature search has been conducted, and
  - Summary of adverse S&E data with citation to the literature

*Content and Format (21 CFR 807.94)

Information Requested (cont.) (21 CFR 807.87)

- Indications for Use Statement
- Truthful and Accurate Statement
- Proposed labeling
- Adherence to voluntary standard
- Financial Certification or Disclosure Statement or both

Information Requested (cont.) (21 CFR 807.87)

- Performance Data (bench, animal, clinical)
- Sterilization, Software and Hardware Information, if any
- Address information requested in specific guidance documents

Clinical Data in 510(k)

- 10-15% of all 510(k)s
- Important difference with the predicate device
- Must be collected under IDE

  (21 CFR Part 812)

FDA Requests Additional Information for:

- Incomplete submissions (Refuse to Accept)
- When testing data is required to demonstrate equivalence

Additional Data (cont.)

- Reviewer request by phone or letter
- Forward to Document Mail Center
- 30 days to submit
- May request extension of time

FDA Review Procedure

- Application Log-in
- Division Acceptance
- Assignment to Reviewer/Review Group
- ODE Review
- FDA Issues Decision letter
- SE Decision Made Public Within 30 days

510(k) Paradigm

- Special 510(k)

- Abbreviated 510(k)

Special 510(k): Device Modification

- Manufacturer modifies own legally marketed device & determines that a 510(k) is required
- Modification does not affect intended use or fundamental scientific technology

Special 510(k): Device Modification

- Manufacturer assesses modification in accordance with 21 CFR 820.30
- 510(k) is submitted with “declaration of conformity” to design controls and summary of design control activities
- Description of modified device and comparison to cleared device
- Previous intended use and new intended use
- FDA processes in less than 30 days

Summary of Design Control Activities

- Risk analysis method(s) used to assess impact of the modification of the device
- Results of risk analysis
- Verification and/or validation activities required (including methods and acceptance criteria)
- Declaration of conformity with design controls

Declaration of Conformity to Design Controls

- Statement that all verification and/or validation activities were preformed and results demonstrate that the acceptance criteria were met
- Statement that manufacturing facility is in conformance with DC procedure requirements
- Statements must be signed by designated individual(s)

Abbreviated 510(k)

- Manufacturer intends to market new "reserved" Class I, Class II or Class III device
- Device is subject to special controls/FDA guidance or standard(s)
- Manufacturer uses special controls/FDA guidance or conforms to standard(s)

Abbreviated 510(k)

- Required elements of 21 CFR 807.87

- 510(k) submitted with summary information on special controls and/or “declaration of conformity” with standard(s)

Confidentiality of Information

- 21 CFR 807.95

Misbranding by Reference to 510(k)

- 21 CFR 807.97

Suggestions

- Submit two copies
- Clearly label what type of 510(k)
- Paginate accurately
- Include Table of Contents
- Include 510(k) Screening Checklist citing page numbers

510(k) Statistics FY's 00, 01 and 02

- 510(k)s Received:
  - FY 00 - 4,204
  - FY 01 - 4,254
  - FY 02 - 4,320
- 510(k)s Logged Out:
  - FY 00 - 4,397
  - FY 01 - 4,148
  - FY 02 - 4,376

510(k) Statistics FY's 00, 01 and 02

- Average Review Times
  - FY 00 - FDA Days 77 Total Days 104
  - FY 01 - FDA Days 74 Total Days 106
  - FY 02 - FDA Days 79 Total Days 100
- Cycles
  - FY 00 - 1.42
  - FY 01 - 1.38
  - FY 02 - 1.39

Appeal Process

- Normally under 21 CFR 10.75
- For any decision
  - hold letter
  - not equivalent
  - policy matter
- May request a meeting
- Will receive written response

Appeal Process (cont.)

- Guidance Available
  - -Medical Device Appeals and Complaints
  - - Resolving Scientific Disputes Concerning the Regulation of Medical Devices
- Status

510(k) Rescission Regulation

- Currently Under Development

- Current Reasons
  - -Significant Public Health Risk(s)
  - -Fraud
  - -Other Compelling Reasons

MDUFMA

- Medical Device User Fee and Modernization Act of 2002
- www.fda.gov/cdrh/mdufma
- Contact DSMICA: (800)638-2041 or (301)443-6597
- Send an email to: MDUFMA@cdrh.fda.gov

MDUFMA (cont)

- First year fee = $2,187 per 510(k)
- Reduced fee to protect small businesses. Small = sales and receipts less than $30 million
- Small business fee for 510(k) starts FY 04
- Sunset October 1, 2007
- No fee for Third Party 510(k)

510(k) Guidance Websites

- The New 510(k) Paradigm
  - www.fda.gov/cdrh/ode/parad510.html
- Frequently Asked Questions and Answers on Paradigm
  - www.fda.gov/cdrh/ode/qanda510k
- Determination of Intended Use for 510(k) Devices
  -www.fda.gov/cdrh/ode/k98-1.html

510(k) Guidance Websites

- General/Specific Intended Use
  - www.fda.gov/cdrh/modact/genspec.html
- Class I Exemption Regulation
  - www.fda.gov/OHRMS/Dockets/98fr/011400a.pdf
- Class II Exemption Regulation
  -www.fda.gov/cdrh/modact/frclass2.html

510(k) Guidance Websites

- Convenience Kit Interim Regulatory Guidance
  - www.fda.gov/cdrh/ode/convkit.html
- Evaluation of Automatic Class III Designation
  - www.fda.gov/cdrh/modact/classiii.html
- Procedures for Class II Device Exemptions from 510(k)
  - www.fda.gov/cdrh/modact/exemii.html

510(k) Guidance Websites

- Deciding when to Submit a 510(k) for a Change to an Existing Device
  -www.fda.gov/cdrh/ode/510kmod.html
- Preamendment Status Determination
  - www.fda.gov/cdrh/preamend.html
- Blue Book Memo: Fax & E-mail Comm.
  - www.fda.gov/cdrh/ode/A02-01.html

510(k) Guidance Websites

- Device Advice
  - www.fda.gov/cdrh/devadvice
- Good Guidance Practices
  - www.fda.gov/cdrh/ggpmain.html
- Medical Device Appeals and Compliants
  - www.fda.gov/cdrh/modact/dispres1.pdf
- Resolving Scientific Disputes Concering the Regulation of Medical Devices
  -www.fda.gov/cdrh/resolvingdisputes/1121.html

510(k) Guidance Websites

- Expedited Review
  - www.fda.gov/cdrh/modact/expedite.html
- Redacted Version of 510(k)s
  - www.fda.gov/OHRMS/DOCKETS/98fr/122199a.txt
- Reuse of Single Use Devices
  - www.fda.gov/cdrh/reuse/index.shtml

FDA Guidance Documents

- Facts-on-Demand:
  1-800-899-0381 (Index is #919)
  301-827-0111
- Division of Small Manufacturers, International and Consumer Assistance (DSMICA) 1-800-638-2041 or 301-443-6597
- Internet: http://www.fda.gov/cdrh

EXHIBIT E
(Filed Under Seal)

Second Supplement Expert Report David A. Kessler, M.D. Para. 23

EXHIBIT F
(Filed Under Seal)

Second Supplement Expert Report David A. Kessler, M.D. Para. 26 Footnotes 15 & 16

Deposition Excerpts, Articles and PRESERVE Letters Remaining documents previously filed by Defendants

EXHIBIT G

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 29 Footnote 17

VIEWPOINT

Data Desert for Inferior Vena Caval Filters
Limited Evidence, Supervision, and Research

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Viewpoint

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Is there enough evidence to support the use of inferior vena caval filters?—No.

The inferior vena caval (IVC) filter is a widely available medical device that has been used for decades to prevent pulmonary embolism (PE), but studies testing the device have not demonstrated adequate proof of efficacy. Venous thromboembolism (VTE) is the third most common vascular disease after myocardial infarction and stroke, while nearly 1 million patients are diagnosed as having fatal or nonfatal PE annually in the United States and Europe combined. Inferior vena caval filters first received approval by the US Food and Drug Administration (FDA) in 1976, the year the FDA was assigned by Congress to regulate medical devices. The approval came with little supervision on the efficacy of these devices, and the devices have remained FDA-approved ever since. The approval of retrievable filters, with theoretical safety advantages but little proof of net benefit, further fueled the use of IVC filters. Recent evidence indicates that 1 in 6 Medicare beneficiaries with PE receive an IVC filter for secondary prevention.[1] The global market of IVC filters should exceed $430 million in 2016.

However, there has been a major disconnect between the widespread use of and evidence base for IVC filters (**Table**). Inferior vena caval filters were approved as class II devices by the FDA, a class of devices that are deemed generally safe, and were approved without the acquisition of data on safety or efficacy. It took nearly 2 decades since their approval until the first randomized trial tested the use of IVC filters, powered for a clinical end point. The Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) trial,[8] a study of 400 patients with proximal deep vein thrombosis randomized to receive anticoagulation with or without IVC filters, demonstrated reduced rates of PE at the cost of increased rates of recurrent deep vein thrombosis, without a difference in mortality at 2- or 8-year follow-up. The second and, to our knowledge, last adequately sized randomized trial of IVC filters, PREPIC II,[9] was published in 2015. This study did not show a mortality reduction in patients with PE at a high risk of recurrence who received a retrievable IVC filter in addition to anticoagulation compared with patients who received anticoagulation alone. The rate of recurrent PE, the study's primary end point, was numerically higher in the group that received IVC filters.[9]

To our knowledge, for the more common indications, such as recurrent VTE despite adequate anticoagulation or contraindications to anticoagulation, there are no randomized trials performed or even planned, with some experts questioning the existence of equipoise in these scenarios. Most of the existing data primarily come from noncontrolled (ie, single group) observational studies and retrospective unadjusted or modestly adjusted observational information from administrative databases, with only a few reasonably sized studies from true VTE registries. This issue becomes more striking when we consider that IVC filter placement is both costly and associated with risks such as malpositining, hematoma, recurrent DVT (in up to 20% of patients), and IVC thrombosis (in 2%-10% of patients).

Despite the paradox between the poor evidence base for the efficacy of IVC filters and the widespread use of the procedure, regulatory authorities such as the FDA had not requested additional data until recently, when safety concerns were raised about IVC filters, particularly the retrievable filters. As a result of concerns raised by the FDA because of reports of more than 900 instances of complications secondary to retrievable filters and others,[10] companies that manufacture the device along with the Society for Vascular Surgery and Society of Interventional Radiology designed the Predicting the Safety and Effectiveness of Inferior Vena Cava Filters study. The study, which recently started patient recruitment, plans to enroll 2100 patients undergoing IVC filter placement from the major device companies available in the United States. Such efforts are commendable, and results of the study will provide more clarity on some aspects of IVC filter use and adverse effects. Nevertheless, this single-arm study is incapable of addressing the efficacy question because the treatment is not being compared with alternatives; the device's effectiveness cannot essentially be tested. Further, interestingly, the study website carries the name of "trial" (http://www.preservetrial.com).

While physicians and even opinion leaders remain uncertain about the usefulness and net benefit of IVC filter use in patients with VTE, there are still few ongoing efforts to better understand the true efficacy of IVC filters. We are similarly unaware of any prior surveys of patients' awareness of the dearth of data in this field. We encourage further advocacy from governing bodies, such as the FDA, payers, and patient advocacy groups to scrutinize the use of IVC filters and to seek further information on not only the safety but also, and more importantly, the efficacy of these devices. The FDA should seek more information on the efficacy of these devices. Payers should also voice their concern about poor efficacy information and potentially adjust their payment policy and seek further studies. Patients, as the ultimate users and owners of the health system, should also actively engage and help activate funding mechanisms that prioritize patient-oriented comparative effectiveness studies.

Table. Evidence Summary and Guidelines Recommendations for IVC Filter Placement

Clinical Scenario	ACCP[2]	AHA[3]	Evidence Base	Comment
Acute VTE with contraindication to anticoagulation	Recommended	Recommended	Initially based on expert recommendation, an adequately adjusted observational study[4] suggested significantly reduced PE-related mortality rates and a trend toward lower all-cause mortality in patients who received IVC filters compared with those who did not.	Further investigation is needed (likely prospective observational) to determine the optimal type and duration of IVC filter use for patients with temporary contraindications.
Recurrent VTE despite adequate anticoagulation	Recommended	Recommended	Based on expert recommendation.	Further investigation is needed (ie, RCTs and/or prospective observational studies).
Massive (ie, hemodynamically unstable) PE	No specific recommendations	May be considered	Based on data from the ICOPER registry[5] that suggested lower rates of 90-d all-cause mortality in a small subset of 11 patients who had massive PE and received an IVC filter.	Further investigation is needed with additional prospective observational studies; an RCT is possible, but it would be difficult to recruit enough patients.
Acute VTE and concurrent poor cardiopulmonary reserve	No specific recommendations	May be considered	No specific studies in this context. The AHA recommendations cite ICOPER data[5] for those with massive PE.	Further investigation is needed (ie, RCTs and/or prospective observational studies).
Acute VTE being treated with thrombolytics	No specific recommendations	No specific recommendations	A study[6] from an administrative database with limited adjustments suggested lower all-cause in-hospital mortality rates in patients with PE who received thrombolytic therapy and an IVC filter compared with those who received thrombolytic therapy alone.	Further investigation is needed (ie, RCTs and/or prospective observational studies). Patients might have massive or high-risk submassive PE or extensive DVT treated with thrombolytics.
Acute VTE in patients with cancer	No specific recommendations	No specific recommendations	A small RCT of 64 patients with VTE and cancer,[7] albeit underpowered, did not show a significant difference in recurrent PE or mortality (although it was numerically higher in the group treated with IVC filters).	Further investigation is needed (ie, RCTs and/or prospective observational studies) to investigate the true efficacy. It would be interesting to compare anticoagulation, IVC filters, and both in the subgroup with cancer and a high risk of anticoagulation.
Acute proximal DVT with no contraindication for antithrombotic therapy	Not recommended	Not recommended	The PREPIC trial[8] showed reduced rates of PE but increased rates of recurrent DVT, without a change in mortality rates.	Routine use of IVC filters in these patients is not recommended.
Acute PE with high risk of recurrence but no contraindication for antithrombotic therapy	Not recommended	Not recommended	The PREPIC II trial[9] did not show a decline in the rates of recurrent PE or mortality.	Routine use of IVC filters in these patients is not recommended.

Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; DVT, deep vein thrombosis; ICOPER, International Cooperative Pulmonary Embolism Registry; IVC, inferior vena caval; PE, pulmonary embolism; PREPIC, Prevention du Risque d'Embolie Pulmonaire par Interruption Cave; RCT, randomized clinical trial; VTE, venous thromboembolism.

ARTICLE INFORMATION

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REFERENCES

1. Bikdeli B, Wang Y, Minges KE, et al. Vena caval filter utilization and outcomes in pulmonary embolism. *J Am Coll Cardiol*. 2016;67(9):1027-1035.

2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. *Chest*. 2016;149(2):315-352.

3. Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. *Circulation*. 2011;123(16):1788-1830.

4. Jiménez D, Muriel A, Monreal M, Yusen RD. Reply: Immortal time bias and the use of IVC filters. *J Am Coll Cardiol*. 2014;64(9):955-956.

5. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation*. 2006;113(4):577-582.

6. Stein PD, Matta F. Vena cava filters in unstable elderly patients with acute pulmonary embolism. *Am J Med*. 2014;127(3):222-225.

7. Barginear MF, Gralla RJ, Bradley TP, et al. Investigating the benefit of adding a vena cava filter to anticoagulation with fondaparinux sodium in patients with cancer and venous thromboembolism in a prospective randomized clinical trial. *Support Care Cancer*. 2012;20(11):2865-2872.

8. PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism. *Circulation*. 2005;112(3):416-422.

9. Mismetti P, Laporte S, Pellerin O, et al; PREPIC2 Study Group. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism. *JAMA*. 2015;313(16):1627-1635.

10. US Food and Drug Administration. Removing retrievable inferior vena cava filters: initial communications. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm221676.htm. Accessed May 22, 2016.

EXHIBIT H

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 31 Footnote 18

Guidance for Industry and FDA Reviewers/Staff

Guidance for Cardiovascular Intravascular Filter 510(k) Submissions

Document issued on: November 26, 1999

This document supersedes document Guidance for the Submission of 510(k) Premarket Notifications for Cardiovascular Intravascular Filters, February 11, 1997.

U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Interventional Cardiology Devices Branch
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Angela C. Smith, Center for Devices and Radiological Health, 9200 Corporate Boulevard, HFZ-450, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Angela C. Smith at (240) 276-4040 or by e-mail at angela.smith@fda.hhs.gov.

Additional Copies

World Wide Web/CDRH home page: http://www.fda.gov/cdrh/ode/24.pdf, or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 024 when prompted for the document shelf number.

Guidance1 for Cardiovascular Intravascular Filter 510(k) Submissions

This guidance document describes a means by which cardiovascular intravascular filter devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate cardiovascular intravascular filter device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

I. Scope:

This draft guidance has been developed in an attempt to identify important preclinical tests and clinical design considerations for cardiovascular intravascular filters (filters). This guidance addresses filters that are permanently implanted in the inferior vena cava for the purpose of preventing thromboemboli generated in the lower limbs from flowing into the right side of the heart and the pulmonary circulation. It is limited in scope to those filters that are designed in such a way as to be seated within the vena cava via a series of hooks which are at the end of several legs or struts which converge at an apex. Filters that have a design that is significantly differs from this may require premarket approval and submission of a premarket approval application (PMA) or a completed product development protocol (PDP). This guidance is further limited to filters indicated for use for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated
- Failure of anticoagulant therapy in thromboembolic diseases
- Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced
- Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated

Manufacturers who wish to pursue other indications should contact FDA to determine the data necessary to support a new indication and the appropriate regulatory pathway.

II. Introduction

Pulmonary embolism (PE) is a serious clinical issue causing significant morbidity and mortality. It has been estimated that more than 600,000 cases of clinically significant PE occur and result in

1 This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

approximately 200,000 deaths annually in the United States[2,3 4]. The patient often survives the first embolism but is at high risk that a second fatal PE will occur. PE recurs in approximately 6% to 25% of treated patients[2]. Additionally, the incidence of PE in patients with deep venous thrombosis (DVT) is 19% to 28%[5]. Treatment of PE has been shown to be effective in reducing the mortality from 30% to 8%[1]. Normally, patients with DVT and, or PE are treated with anticoagulation therapy. However, in some patients anticoagulation is ineffective, contraindicated or results in complications which require that it be discontinued. For these patients, vena caval interruption with a filter is recommended. The goal of filter placement is to try to obtain high filtering efficiency (large and small emboli) without impedance of blood flow and with reduced device related thrombosis while minimizing migration and without penetration of the vessel wall.

The following are the criteria for an ideal filter:

- Nonthrombogenic
- High filter efficiency without impedance of blood flow
- Secure fixation within the vena cava
- Rapid and safe percutaneous insertion
- Low rate of associated morbidity
- Magnetic resonance imaging (MRI) compatibility

The necessary array of tests for a particular filter will depend, in part, on the specific design. Therefore, this document may not reflect the complete battery of pre-clinical testing necessary to qualify all filters/designs. However, there are certain aspects of filter design that are general in nature and should be assessed. The degree to which a proposed device is similar to a currently marketed filter will indicate the level of testing necessary, i.e., whether the design characteristics can be assessed via *in vitro* bench testing, *in vivo* animal testing, clinical testing or some combination of all three.

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[2] Dalen, J.E. and J.S. Albert, "Natural history of pulmonary embolism," *Progressive Cardiovascular Diseases*, 17:259-270,1975.

[3]Smith B.A., "Vena Caval Filters," *Emergency Medicine Clinics of North America*, Vol. 13, No.3:645-654,1994.

[4] Nunnelee, J.D., and A. Kurgan,"Interruption of the inferior vena cava for venous thromboembolic disease," *Journal of Vascular Nursing*, 11:80-2,1993.

[5]Mohan, C.R., J.J. Hoballah, W.J. Sharp, T.F. Kresowik, C.T. Lu and J.D. Corson, "Comparative efficacy and complications of vena caval filters," *Journal of Vascular Surgery*, Vol.21 No. 2:235-246,1995.

III. Pre-Clinical Testing

A. Biocompatibility

Biocompatibility testing should be conducted in accordance with FDA guidance document "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", which includes an FDA matrix that designates the type of testing needed for various medical devices. Cardiovascular intravascular filters are defined as permanent implant, blood-contacting devices.

B. Filter Performance

Below is an outline of the general issues that need to be addressed when seeking premarket clearance for a filter. It is the submitter's responsibility to conduct testing which adequately addresses the concerns outlined below as well as any others which may arise due to the unique design of the given device. The goal of this outline is to identify the objective(s) of the pre-clinical test. Test protocols and acceptance criteria for these tests are the responsibility of the submitter. FDA recognizes that there are many different testing methods that may be used to satisfy the objective(s). Where appropriate, some of these tests may be combined. These tests may best be carried out in bench top models or in animal models or in a combination of both. FDA advises that prior to the initiation of animal studies, the submitter should contact FDA and discuss the proposed animal study to ensure general agreement on the adequacy of the animal study protocol.

All tests should be performed on filters fabricated by representative manufacturing processes. An adequate number of samples should be tested. The objectives, test methodologies, results, and conclusions should be clearly defined for each test performed. The performance specifications, test conditions and acceptance criteria for all tests should be completely explained and justified by comparison to expected clinical conditions. Where appropriate, testing should be conducted in an environment simulating clinical conditions. The results of all tests should be reported in a statistically meaningful format, i.e., specification of the number of samples, range of values, mean, standard deviation, and a 95 percent confidence interval where appropriate. A probability measure that is indicative of the statistical significance of any comparisons made should be provided.

1. Simulated deployment

An assessment of the ability to completely deploy the filter reliably in the chosen location under simulated clinical conditions should be made. This test should take into consideration the various routes by which the filter can be introduced into the patient, e.g., femoral, jugular, etc. Although it is recognized that the left femoral route is the most tortuous, all labeled routes should be examined.

2. Introducer/sheath suitability

The objective(s) of this test should be to demonstrate that the sheath will adequately resist kinking when used in the most tortuous pathway. In addition, all bonds of the introducer/sheath should be assessed for their pull strength.

3. Clot trapping ability

This test should demonstrate that the device can capture clinically significant emboli yet still permit sufficient blood flow around trapped emboli without caval occlusion. It should also examine whether the filter achieves this efficiency immediately post-deployment. If it does not, the time period necessary to achieve full filtering efficiency should be characterized.

4. Filter fracture

The filter's response to worst-case respiratory and diaphragmatic movements in the vena cava under simulated respiratory cycles should demonstrate sufficient fatigue resistance of the filter design. In addition, there should be an examination of corrosion resistance and weld strength following cycling.

5. Caval perforation/filter migration

This test should demonstrate that the filter fixes itself within the vena cava at the deployment site and undergoes sufficient endothelialization. The force necessary for device fixation should be characterized over the range of labeled inferior vena cava (IVC) diameters. In addition, this force should not suggest a tendency to perforate the caval wall.

6. Thrombogenicity

The thrombogenic potential of the filter should be examined. This test should demonstrate that the effect of the device on the blood flow would not be sufficient to cause stasis, which could lead to thrombus formation in and around

the device.

7. MRI compatibility

The extent to which the filter is compatible with MR imaging should be assessed (see the Attachment).

IV. Clinical Investigations

It is anticipated that human clinical investigations could be necessary in the development of a "new" vena cava filter to establish its equivalency to currently marketed filters. Such a study may also be necessary for a modified filter design. The need for such a study should be discussed with FDA prior to submission of an investigational device exemption (IDE) application. In those cases in which a study is deemed necessary, the sponsor should carefully consider the following items:

- the appropriate study design
- the study hypothesis
- appropriate sample size
- definitions of success and failure
- the clinically relevant endpoints necessary for the demonstration of substantial equivalence

For the indications outlined previously, the risks and benefits to the patients are well documented. The intent of the clinical study should be to demonstrate that the rates of complications for the investigational filter are comparable to other marketed vena cava filters. Although the risks themselves are well described in the literature, the definitions and methods used to determine the rates are inconsistent and highly variable. Therefore, it is critical to prospectively define and identify the methods of analysis for each potential complication. The complications identified and analyzed during the course of the clinical investigation should include the following:

1. Complications during filter insertion

In the course of trying to place the filter in the vena cava the following

complications have been noted[6,7]:

- Sheath perforation
- Introducer tip detachment
- Guidewire kinking
- Sheath kinking

These complications can result in[8]:

- Filter deformation
- Fracture
- Premature release or insufficient opening
- Improper placement
- Thrombus formation which may result in insufficient opening

There have also been reports of problems with[9]:

- Filter sticking to and/or getting caught in the introducer while the device is being deployed
- Practitioner difficulty with inserting and/or retrieving failed insertions of the device
- Filter legs breaking during insertion
- Deployment within the introducer
- Breakage of the filter /filter legs upon placement of the device in the patient

The protocol should identify these potential complications and ensure that they will be captured by the investigator on the appropriate data collection forms.

2. Recurrent pulmonary embolism

Patients who present with symptoms suggestive of recurrent PE should undergo a lung scan and/or an arteriogram. If recurrent PE is confirmed, a contrast vena cavogram should be performed to check for any clot within the filter. Some of the

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[6]Becker, D.M. et al., "Inferior Vena Cava Filters Indications, Safety, Effectiveness," *Archives of Internal Medicine*, 152:1985-1994,1992.

[7]Greenfield, L.J., et. al., "Extended evaluation of the titanium Greenfield vena caval filter," *Journal of Vascular Surgery*, September 1994:458-465.

[8]Bergqvist,D.,"The Role of Vena Caval Interruption in Patients with Venous Thromboembolism," *Progress in Cardiovascular Diseases*, 37(1):25-37,1994.

[9] FDA MDR database

mechanisms, which may be responsible for PE after filter insertion, are the following [8]:

- Ineffective filtration
- Continuous growth of trapped thrombi through the filter
- Development of thrombosis on the proximal end of the filter
- Filter migration to a position where it does not function optimally
- Filter retraction from the caval wall at thrombus retention (occurring if some of the hooks have grasped the thrombus, which creates a channel between the filter and the caval wall)
- Embolization through collaterals that may be lumbar
- Embolization that may occur via the ovarian/spermatic veins
- Embolization from thrombi proximal to the filter (arm veins, renal or hepatic veins, the right heart)
- Incorrect position of the filter

For those patients who experience a recurrent PE, every attempt should be made to determine the probable mechanism.

3. Death

Deaths attributable to filter complications have been reported to result from:

- cardiac arrest immediately following filter placement
- misplacement of the filter during insertion
- cephalic migration of a filter to the heart after placement.

All patients with suspected filter complications who died during the clinical investigation should undergo an autopsy. A complete report of the findings should be provided for review.

4. Filter migration

Minor filter migration in the caudal or cephalic direction is commonly reported and does not appear to be associated with clinically significant events. The walls of the vena cava are known to move with respiration and changes in intra abdominal pressure induce flexion on the limbs of the filter. The filter may appear to have migrated due to x-ray equipment variation, patient position, measurement error, and respiration. Much of the reported filter movement may actually be due to measurement error resulting from differences in patient positioning, breathing, and parallax. True migration may be caused by an excessively large vena cava, inadequate positioning and massive embolization into the filter with caval dilatation [8]. It is recommended that any movement of the filter with relation to the spine that is 5 mm or greater be recorded as filter migration. Assessment of distal migration should be determined from post implant and follow-up anterior-posterior and lateral films after correction for magnification. When follow-up images are

obtained, efforts should be made to closely reproduce patient positioning and patient respiration to reduce errors in the interpretation of filter migration.

5. Caval penetration

Determination of caval penetration is complicated. Examination via cavography may show filter hooks or legs outside the flow of contrast. This is not necessarily due to penetration. It may be due to endothelialization or tenting of the vena cava or locations in tributary veins. Computed tomography (CT) scans can be used to help rule out some false positives. After correction for magnification, filter base diameter from hook to hook should be recorded from both the implant and follow-up plain films. If an increase in filter base diameter of $\geq$ 5 mm is recorded, a CT scan should be performed to confirm or exclude the position of filter legs outside of the inferior vena cava. Any other changes, which may be suggestive of possible filter leg penetration of the vena cava, should trigger a CT scan, regardless of increase in the filter base diameter.

6. Filter tilting and angulation

The significance of tilting and angulation of caval filter after placement is controversial. There is a theoretical loss of filtering efficacy of any filter when tilted or angulated significantly; however there is no good clinical data to support a definite increased incidence in PE or failure to trap thrombi. All instances of tilting or angulation should be noted as well as any associated clinical sequelae.

7. Caval occlusion

Caval occlusion is related to filter thrombogenicity, design and flow patterns[8]. Small or moderate sized emboli trapped in a filter are usually asymptomatic since the residual patency of the vena cava and the normal paravertebral collateral veins permit adequate venous return. A large trapped embolus or a cluster of small emboli may occlude a filter completely and thus block the vena cava. After a period of days or weeks, the occlusion occurs and causes a sudden swelling of both lower limbs. In almost all cases the symptoms of IVC occlusion are transient and resolve almost completely within a few weeks or a few months since the thrombi undergo spontaneous lysis. Since it is often clinically difficult or impossible to distinguish IVC filter occlusion from extension of the preexisting DVT because the symptoms may be similar, all instances should be recorded as occlusion unless the extension of DVT can be ruled out.

8. Filter embolization

The risk of filter embolization is primarily limited to the first two weeks after implantation. Embolization of the filter is a serious complication with variable clinical

consequences, comparable to pulmonary thromboembolism. These range from being totally asymptomatic to sudden death. Therapy also ranges from no therapy to open chest surgery and removal of the device. All cases of filter embolization should be recorded and the reasons for occurrence immediately assessed. The subsequent treatment should also be described in detail.

9. Other risks

Complications that occur at the puncture site such as: hematoma formation and A-V fistula, DVT at the puncture site, pneumothorax and air embolism after jugular insertion, should all be recorded on data collection forms and analyzed.

IV. Labeling

The Division of Cardiovascular, Respiratory and Neurological Devices (DCRND) of the Office of Device Evaluation (ODE) conducted a review of the labeling for marketed cardiovascular intravascular filters (vena cava filters). Based on that review, the Food and Drug Administration (FDA) believed that several changes should be made to existing labels to ensure consistency among device manufacturers and to facilitate appropriate use of the devices clinically.

The following sections of the labeling were affected:

- Indications for use
- Contraindications
- Warnings

The Attachment contains a copy of the labeling format developed for this device.

ATTACHMENT

INDICATIONS FOR USE

The labeling should include the following text:

The [NAME OF DEVICE] is indicated for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations:

- **pulmonary thromboembolism when anticoagulants are contraindicated;**
- **failure of anticoagulant therapy in thromboembolic diseases;**
- **emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; and**
- **chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated.**

CONTRAINDICATIONS

The labeling should include the following contraindication:

Vena Cava filters should not be implanted in patients with risk of septic embolism.

Your labeling may include other contraindications which are specific to your particular device design.

WARNINGS

The labeling should include information regarding the use of the device in patients undergoing magnetic resonance imaging (MRI). The following terminology should be used:

MRI-Safe: No additional risk to the patients, but may affect the quality of the diagnostic information.

MRI-Compatible: MRI-Safe and neither interferes with nor is affected by the operations of a MRI device.

Non-Compatible: Neither MRI-Safe nor MRI-Compatible and should not be used in conjunction with MRI systems.

Data to support the chosen warning should be included in your 510(k) notification.

EXHIBIT I

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 34 Footnote 19

The Regulation of Medical Devices

Robert Gatling, Jr.
Director, Program Operations Staff
Office of Device Evaluation
Center for Devices and Radiological Health
5/2009

Outline

- Statutory Acts
- Definition of a Device
- Device Classification
- Section 510(k) & Purpose
- Premarket Approval (PMA)
- Investigational Device Exemption (IDE)
- Humanitarian Device Exemption (HDE)
- Safe Medical Devices Act of 1990
- FDA Modernization Act (FDAMA) 1997
- Medical Device User Fees 2002 &2007

Statutory Acts

http://www.fda.gov/cdrh/lawsregs.html

- Pre 1976 – Devices regulated under drug authorities
- May 28, 1976 - Medical Device Amendments (PL 94-295)
- Safe Medical Devices Act (SMDA) of 1990
- FDA Modernization Act (FDAMA) of 1997
- Medical Device User Fees Acts of 2002 & 2007

Definition of a Device (201(h))

- an instrument, apparatus, implement, machine, contrivance implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -
- (1) recognized in the official National Formulary, or the US Pharmacopeia, or any supplement to them

Definition of a Device (cont)

- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- (3) intended to affect the structure or any function of the body of man or other animals, and

Definition of a Device (cont)

- which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

  (201(h))

Device Classification

- Device Classes
  - Class I - General Controls - 43%
    - 91% Exempt from 510(k)
  - Class II - Special Controls - 51%
    - 7% Exempt from 510(k)
  - Class III - Premarket Approval - 6%
- 1870+ Device Categories
- 18 Classification/Advisory Panels
- Transitional Devices

General Controls

- Adulteration and Misbranding (501&502)
- Registration,Listing, & 510(k) (510)
- Banned Device (516)
- Notification and other Remedies (518)
- Records & Reports (519)
- Quality Systems Regulation (520)

Special Controls

- Standards
- Post-market Surveillance
- Patient Registries
- Guidelines
- Recommendations
- Other as Necessary

Section 510(k) of the Act

- Established 90 day timeframe
- Format by Regulation
- Device Class
- Action to comply with Section 514 and 515
- Implementation of Section 510(k)
  - 21 CFR Section 807 Subpart E

Purpose of 510(k)

- Demonstrate “substantial equivalency”
- Clearance to market

510(k) Review Guidance http://www.fda.gov/cdrh/devadvice/314.html

- Blue Book Memo - K-86-3
  - http://www.fda.gov/cdrh/k863.html
- 510(k) Decision Tree
- Device Specific Guidance
  - http://www.fda.gov/cdrh/guidance.html
- Format for 510(k) Guidance
  - http://www.fda.gov/cdrh/ode/guidance/1567.pdf

Devices Which Need a PMA

- "New Devices"
  - Premarket Notification
    - Not Substantially Equivalent
  - Post Amendments Devices
- Transitional Class III Devices
  - Previously Regulated as New Drugs

Transitional Devices

- Some were classified:
  - Gauze
  - Adhesive Tape
  - Tampons
  - Dialysis Fluid
  - Denture Cushions

Transitional Devices (Cont'd)

- Others remain in Class III
  - Injectable Silicone
  - Adsorbable Sutures (some reclassified into class II)
  - Adsorbable Dusting Powders
  - Injectable Teflon
  - Soft Contact Lenses (reclassified into Class II)

Devices Which Need or Will Eventually Need a PMA

- Pre-Amendments Class III Devices
- SE Post-Amendment Class III Devices
- < 25 device types remaining

Premarket Approval
http://www.fda.gov/cdrh/devadvice/pma/

- Class III Devices are Subject to Premarket Approval
- Reasonable Assurance Safety and Effectiveness
  - Valid Scientific Evidence
  - Risk/Benefit

    vs
  - Substantial Equivalence

Safety and Effectiveness

- Considerations
  - Persons for whose use the device is intended
  - Conditions of use of the device
  - Possible benefit to health vs probable injury or illness from use
- Reliance on Valid Scientific Evidence Only

Investigational Device Exemption
http://www.fda.gov/cdrh/devadvice/ide/index.shtml

- Intent to study:
  - New intended use of approved device; or
  - New device
- Physician may be Investigator & Sponsor
- FDA approval of an IDE application required?
  - Significant Risk (SR) study -- yes
  - Non-significant Risk (NSR) study -- no

Significant Risk?

Presents a potential for serious risk to the health, safety, or welfare of the subject and may be:

- An implant;
- Life supporting/life sustaining;
- Of substantial importance in diagnosing, curing, mitigating, or treating disease; or,
- Otherwise presents potential for serious risk.

Significant Risk -- Who Decides?

http://www.fda.gov/cdrh/d861.html

- Sponsor (Sponsor/Investigator (S/I) or firm) presents their determination to IRB
- IRB agrees, consults, or defers
- FDA - ultimate authority

⇨ If uncertain, use SR/NSR Guidance and/or consult with IDE Staff

Non-Significant Risk vs Significant Risk

NSR

- IRB approval
- Informed Consent
- Examples (later)

SR

- IRB approval
- Informed Consent
- *FDA approval*
- 30 Day Review/Letter always sent
- CMS Reimbursement Code
- Examples (later)

Non-Significant Risk Devices
http://www.fda.gov/cdrh/d861.html

- Daily wear contact lenses
- Conventional endoscopes
- Dental filling material
- General biliary & vascular catheters
- TENS devices for pain
- Most wound dressings

Significant Risk Devices

http://www.fda.gov/cdrh/d861.html

- Vascular & therapeutic catheters
- Anesthesia machines
- Epidural & spinal catheters
- Dialyzers
- Implants
- Contraceptive devices
- Extended wear contact lenses

Humanitarian Device Exemptions (HDEs)

http://www.fda.gov/cdrh/devadvice/hde.html

- For diseases/conditions affecting less than 4,000 patients in US per year
- No approved alternative device
- Exemption from effectiveness requirement of the Act
- Is a marketing approval
- 75-day review clock

HDE Examples

- Implantable Replacement Heart
- Right Ventricular Assist System
- Ventricular Septal Defect Occlusion System
- Bladder Stimulator for Urination on Demand
- Finger Prosthesis for Patients with Painful Osteo-Arthritis
- Fetal Bladder Stent
- Urological Stimulator for Children with Neurogenic Bladder due to Spina Bifida
- Vertical Expandable Prosthetic Titanium Rib

"Off-label" Use of Devices

- "Practice of Medicine" Policy states that a physician should:
  - Be well informed about the product
  - Use firm scientific rationale and sound medical evidence
  - Maintain records on use and effects
- IDE not req'd; IRB/IC approval may be

Safe Medical Devices Act of 1990 (SMDA)

- Expanded 1976 authorities
  - Codified FDA practice on 510(k) decision practices
    - http://www.fda.gov/cdrh/ode/655.pdf
  - Truthful and Accurate
  - Summary/Statement
  - Class III Summary
  - Required clearance order before marketing

FDA Modernization Act (FDAMA) - 1997

http://www.fda.gov/cdrh/modact/modguid.html

- 3rd Party Review
- Exemptions for Class I & II
- Labeled Intended Use
- Evaluation of Automatic Class III Designation (De Novo)
- Recognize Standards
  - Over 750 recognized as of 9/08
- Least Burdensome (10/4/02 Guidance)

Examples of De Novo Devices

- Air-conduction Hearing Aid
- Swallowable Imaging System
- Heimlich Maneuver Assist Device
- Sulfide Detector for Periodontal Disease
- Laser for Fluorescence Caries Detection
- Several In Vitro Diagnostic Devices
  - West Nile Virus antibody ELISA
  - Influenza Nucleic Acid Assay
  - Malaria Test

Medical Device User Fee and Modernization Act of 2002 (MDUFMA)

http://www.fda.gov/cdrh/mdufma/

I. User Fees
II. Performance Goals
III. Third-Party Inspections
IV. Reprocessed Single-Use Devices
V. Additional Provisions

Applications/Submissions Subject to Fees (updated for 2007 law)

- Premarket Application (PMA and PDP)
- Premarket Report
- Panel Track Supplements
- 180-day Supplements
- BLA & Efficacy Supplements
- Real-time Supplements
- 30-day Notice
- PMA Annual Report
- Premarket Notification [510(k)] Submissions
- 513(g) Request for Information
- Device Registration

Exceptions to user fees

- Humanitarian Device Exemption
- Further Manufacturing Use Supplements
- State and federal sponsors (non-commercial)
- 510(k) submissions reviewed by third parties
- PMA or 510(k) Pediatric Only Conditions of Use
- Investigational Device Exemptions (IDEs)

Performance Goals

- General Goal of User Fees
  - To support an improved review process through added resources resulting in more predictable and timely approval/clearance of safe and effective products

Performance Goals (continued)

- General Comments
  - Goals are defined in letter from DHHS Secretary to Congress
  - Based on decision goals
  - Measured in FDA days
  - Separate goals for each submission type

What is the Purpose of Third Party Inspection?

http://www.fda.gov/cdrh/ap-inspection/index.html

- FDA will have greater flexibility to use its limited inspectional resources
- Industry will have ability to schedule AP and other conformity assessment body (CAB) inspections simultaneously

Reprocessed Single-Use Devices

- Reprocessed single-use device must be "prominently and conspicuously" labeled:

  Reprocessed device for single use. Reprocessed by [name of manufacturer that reprocessed the device]
- New type of premarket submission, the *premarket report*, with additional data requirements that focus on reprocessing for Class III devices
- Validation Data Required

Additional Provisions

- Electronic Labeling
- Modular Review of PMAs
- Pediatric Use
- Combination Products

MDUFA of 2007

- Updating of goals and fees provision of MDUFMA
- Eliminated cycle goals – only decision goals
- Some new provisions

FY 08 Submission Numbers

- 510(k)s received
  - Originals 3,848
- PMA received
  - Originals 31
  - Supplements (all types) 1,552
- IDEs received
  - Original 221
  - Supplements 4,439

EXHIBIT J

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 35 Footnote 20

SPECIAL ARTICLE ARCHIVE

The Federal Regulation of Medical Devices

David A. Kessler, M.D., J.D., Stuart M. Pape, J.D., and David N. Sundwall, M.D.

N Engl J Med 1987; 317:357-366 | August 6, 1987 | DOI: 10.1056/NEJM198708063170606

BEFORE 1976, medical devices could be marketed without review by the U.S. Food and Drug Administration (FDA). Periodic attempts to regulate some devices as drugs for which the agency did require premarketing clearance proved to be cumbersome and inadequate. Spurred by the increased technological complexity of devices and mounting disclosures of shortcomings involving pacemakers, intrauterine devices, and intraocular lenses, Congress enacted the comprehensive Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act.[1 2 3 4] The primary purpose of the amendments was to ensure that new devices were safe and effective before they were marketed.

In the past few years, the FDA has been severely criticized for its implementation of the amendments.[5 6 7 8 9 10 11] A rethinking is now in order. The widening gap between Congress's expectation, as reflected in the specific statutory requirements, and the actual implementation of the law must be examined.[12 13 14 15 16] The failure of the FDA to implement several major statutory provisions intended to ensure the safety and effectiveness of medical devices leads to one of two conclusions: either the safety and effectiveness of medical devices are not being ensured or the provisions are superfluous.

Furthermore, although the need to ensure that medical devices are safe and effective is as great now as it was in 1976, dramatic changes have occurred in the health care environment, especially with respect to Medicare reimbursement by the Health Care Financing Administration (HCFA), that could profoundly affect the research, development, and availability of medical devices. Multiple federal regulatory hurdles must now be overcome before a new medical device can be marketed.

REGULATORY PROCESS

Statutory Framework

The statutory definition of a "medical device" is all-encompassing. Essentially, any item promoted for a medical purpose that does not rely on chemical action to achieve its intended effect is considered to be a medical device.[17] In vitro diagnostic tests are also regulated as medical devices. This broad definition gives the FDA jurisdiction over a wide variety of products — from chewing gum that contains an abrasive food additive for its antiplaque properties to software that analyzes the output of a cardiac monitor.[11 , 18 , 19] Altogether, there are more than 1700 different types of medical devices, 50,000 separate products, and 7000 manufacturers of such devices.[10]

In drafting the 1976 amendments, Congress divided medical devices in two different ways: (1) according to three classes — Class I, II, or III — on the basis of the principle that the more potentially hazardous a device is, the more rigorous the regulatory requirements ought to be,[20 21 22 23 24] and (2) according to seven basic categories — pre-amendment, post-amendment, substantially equivalent, implant, custom, investigational, and transitional (Table 1).[25 , 26] Not surprisingly, a complex regulatory scheme has emerged from the attempt to weave these two methods of subdivision into a workable statutory framework. Unlike the regulation of new drugs, in which standards of safety and effectiveness are applied uniformly, the regulation of devices is based primarily on risk.

TABLE 1

Categorization of Medical Devices under the Medical Device Amendments of 1976.

Class I devices — the least regulated class — require manufacturers to comply with regulations regarding registration, prémarketing notification,[27] record keeping,[28] labeling,[29] reporting of adverse experiences,[30] and good manufacturing practices; these regulations, which are known collectively as general controls, apply to all three classes of devices.[31] Class II devices are

required to meet federally defined performance standards.[32] [33] [34] Class III devices are subject to the most extensive regulation, and they cannot be marketed until the manufacturer demonstrates their safety and effectiveness to the FDA's satisfaction.[35] On petition from a manufacturer, a device may be considered for reclassification into a less-regulated class.[36]

Pre-amendment devices are assigned to the least-regulated class that is sufficient to provide reasonable assurance of safety and effectiveness. Post-amendment devices that are deemed "substantially equivalent" to pre-amendment devices are assigned to the same class as their comparable pre-amendment devices and may be marketed after the manufacturer provides the FDA with premarketing notification. Post-amendment devices not deemed substantially equivalent are automatically assigned to Class III.[37] Pre-amendment Class III devices and their substantially equivalent counterparts may remain on the market until the FDA takes specific regulatory action; post-amendment Class III devices cannot be marketed until the FDA grants premarketing approval.[38]

In practice, there are two main routes to the market for a new device. If the manufacturer can establish substantial equivalence, premarketing notification is all that is required. Otherwise, full premarketing testing and approval are required.

Premarketing Approval

Securing FDA approval of a new device before marketing requires that the manufacturer provide reasonable assurance that the device is safe and effective when used for the purpose for which the approval is sought.[39] [40] [41] [42] Safety and effectiveness are assessed with specific reference to the uses for which the device is intended, as set forth in the labeling on the device.[41] , [43] , [44] Safety is evaluated by weighing the probable benefits to health against the probable risks of injury. The risk –benefit ratio must be acceptable, but proof that the product will never cause injury or will always be effective is not required.[45]

This statutory standard is less rigorous than the standard for the approval of new drugs.[20] , [46] For drug approval, adequate well-controlled investigations by qualified experts are required. For devices, data from well-controlled scientific studies are acceptable, but so is "valid scientific evidence" from which experts can reasonably conclude that the device will be effective.[47] Mere anecdotal medical experience is not sufficient.[45]

An FDA-approved Premarket Approval Application (PMA) is an individual license that allows only the applicant to market the device. Thus, for example, each manufacturer of a magnetic resonance imaging unit must submit a separate PMA, with data adequate to support approval.[41] Data from other PMAs cannot be used without the express consent of the manufacturers who submitted those applications. This policy preserves each manufacturer's competitive edge by guarding its investments in research and development[48]; it can also make premarketing approval more attractive than premarketing notification because it requires that other manufacturers also surmount the hurdle of the PMA. Unfortunately, the policy also fosters the duplication of investigational efforts and raises ethical and practical questions about the performance of unnecessary trials. For this reason, the FDA does not require the duplication of data from other PMAs that have been generally accepted by the medical community, especially when those data have been published. Although several compromises have been proposed with regard to the confidentiality of data in PMAs, none have been adopted.[49] [50] [51] [52]

The premarketing approval process is lengthy.[53] , [34] Although the law requires the FDA to approve or deny a complete application within 180 days, the FDA actually takes an average of a year to approve a PMA.[55] Poorly prepared applications lead to even longer delays.[51] , [55] Specific guidelines for certain types of devices have expedited the process.[55] The FDA recommends that contact with the agency be established early in the development of a medical device.[41] , [51] The sooner deficiencies are identified, the more easily they can be corrected.[55]

Congress had little difficulty in deciding to impose a requirement for premarketing approval on new Class III devices. Pre-amendment Class III devices created more difficulty.[56] Blanket statutory approval of these devices was not appropriate, since problems associated with their use had come to the forefront during debate on the legislation.[25] Instead, Congress tossed the ball to the FDA by allowing pre-amendment devices to remain on the market until the FDA required that PMAs be submitted.[45] The statute does not say when the FDA must call for data on preamendment devices; it only states that the FDA cannot ask for these data until 30 months have passed since the final assignment of the device to Class III. The FDA took one step toward regulating pre-amendment devices several years ago when it announced plans to begin to require premarketing approval for 13 high-priority pre-amendment Class III devices.[57] Even this limited review will stress the FDA's resources considerably, since the 13 device categories will result in an estimated 165 PMAs from manufacturers. To date, the FDA has called for data on only five pre-amendment Class III devices. At the current pace, we will be well into the next century before PMAs are required for all pre-amendment devices.

Substantial Equivalence

The decision to include a "substantial equivalence" provision in the statute was made to ensure fair treatment of post-amendment devices that were similar to pre-amendment devices, as well as to

limit the number of new devices that would require premarketing approval.[58] [59] [60] Little did Congress realize what a profound effect this provision would have on the regulatory scheme of the statute.[11]

The simplest and quickest route to marketing a medical device is to claim that the device is substantially equivalent to one marketed before the 1976 amendments were passed.[58, 60] Approximately 55 "substantially equivalent" premarketing notifications are filed for each PMA.[61] The average FDA response time to premarketing notification is one fifth the response time to a PMA.[62] Under section 510(k) of the amendments, a manufacturer of a substantially equivalent device must notify the FDA of its intention to market the device.[63] [64] [65] If there is no objection by the FDA within 90 days of the receipt of this "510(k) notice," the device may be marketed.

The term "substantial equivalence" is not defined by the law. Congress apparently intended it to accommodate changes in a device that do not affect its safety and effectiveness. The expansive reach of the 510(k) provision is illustrated by the FDA's treatment of the new bioengineered in vitro diagnostic devices. The technology used in the manufacture of devices such as the in vitro test kits for chlamydia and herpesvirus did not exist before the amendments were enacted, yet more than 50 of these devices have been deemed to be substantially equivalent to pre-amendment devices. The reason is that the results of tests of post-amendment devices were substantially equivalent to those of pre-amendment devices. The use of new technology in the assay systems did not preclude a finding of substantial equivalence.[18, 66]

In the past, virtually identical devices have not always been treated consistently. For example, although PMAs were required for ophthalmic uses of the yttrium–aluminum–garnet (YAG) laser, only 510(k)s were required for other uses of the device. Some have argued that the standard should be one of substantially equivalent performance, even if methods and physical characteristics differ. Others argue that the mechanism of action and the physiologic effect should be similar to sustain a claim of substantial equivalence.[58] Not until 1986 did the FDA articulate criteria by which to judge a claim of substantial equivalence. Under the new policy, postamendment devices that have new intended uses require PMAs. Post-amendment devices that have intended uses similar to those of pre-amendment devices may be found to be substantially equivalent only if the new technological features of the device can be shown through descriptive, performance, and even clinical data not to diminish its safety and effectiveness.[67]

Investigational Devices

In the course of developing a medical device, a sponsor may need to conduct clinical studies to support a PMA or, in some instances, a 510(k) submission.[68, 69] Like an investigational-new-drug application, an Investigational Device Exemption (IDE) allows an unapproved device to be distributed and used for investigational purposes.[70] The requirements for an IDE are designed to ensure that the sponsor conducts adequate preclinical testing, selects appropriate subjects for clinical research, obtains informed consent, uses qualified investigators, monitors the investigation, and collects the data promptly.[71, 72] Every investigation of an important new use, even for a device already approved for other uses, requires an IDE.[72]

Congress's aim in correlating risk with degree of regulation is evident with respect to investigational devices.[73] Sponsors of investigations of devices posing "significant" risks must submit an investigational plan to both a local institutional review board, which is itself subject to FDA regulations, and to the FDA; sponsors of investigations of devices posing "nonsignificant" risks need only submit a plan to the institutional review board.[74] The institutional review board makes the initial decision about whether a device poses a significant risk. The FDA can overrule the decision of the institutional review board, but it is generally unaware of studies of devices posing nonsignificant risks. Recently, the FDA has released guidelines to help institutional review boards decide on the degree of risk posed by a device; devices that have the potential to harm patients must be considered to pose significant risks.[75] For example, the FDA concluded that a clinical study of a pacemaker that is a modification of a commercially available pacemaker poses a significant risk because the use of any pacemaker presents a potential for serious harm, even though the modified pacemaker may represent less risk or only slightly more risk in comparison to the available model.

In deciding whether to allow an IDE, the FDA focuses on how the investigation will be conducted rather than on a precise risk–benefit analysis. In the case of the artificial heart, for example, the agency insisted that appropriate preclinical testing be undertaken and the resulting data be reviewed, that the study be scientifically sound, that data collection be complete, and that informed consent be appropriately obtained. Even after much public debate, it remains extraordinarily difficult to answer the question of whether the benefits of implanting the device outweigh the risks.[76, 77]

Emergency and Nonapproved Uses

In 1985, the emergency implantation of a non-FDA-approved artificial heart after a human heart transplant failed drew national attention.[78] Recent FDA guidelines stress that the agency would not object to the use of a potentially lifesaving unapproved medical device if the physician who used it could demonstrate retrospectively that a life-threatening emergency that required immediate treatment existed, that no generally acceptable alternative for treating the patient was available, and that there was reason to believe that the use of the device would benefit the patient. The physician must also be able to demonstrate that time did not permit compliance with existing FDA procedures

for approval of the device, that reasonable foresight on the part of the physician in securing an IDE would not have avoided the problem, and that the physician followed as many procedures for patient protection as possible.[79 , 80] Furthermore, the FDA does not permit the emergency use of an unapproved device by physicians who have had no previous experience with the device.

Use of an approved device for an unapproved use in a nonemergency situation represents a complex legal issue. The safety and effectiveness of medical devices are assessed and approved with specific reference to their intended uses, and their approval is limited to these uses. The FDA will intervene if the device is being commercially promoted for an unapproved use. If the device is to be used as part of a research endeavor, the FDA will require a formal investigational trial. However, a physician who uses a device in an unapproved manner to treat a particular patient, without promoting it for such use, is unlikely to be in violation of the statute. The amendments focus on products, not procedures. As it did with past food and drug legislation, Congress steered away from directly regulating medical practice. However, the very nature of regulatory schemes regarding drugs, devices, and biologic products, coupled with the risk of liability, inevitably restricts practitioners.

Regulation of Medical Devices through Reimbursement Decisions

In the past, manufacturers of devices focused on obtaining FDA approval, but with national attention shifting toward containing health care costs, manufacturers must now also focus on reimbursement regulations.

Decisions made by the HCFA on Medicare reimbursement for new medical devices involve two separate issues — coverage and payment. The issue of coverage involves whether the HCFA will pay for the new device.[81 , 82] The Social Security Act, which establishes the rules for the Medicare program, prohibits payments for any items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury."[83] The HCFA has stated that Medicare will cover an item or service that is generally accepted by the professional medical community as an effective treatment for a particular condition; payment will also be made if the safety and effectiveness of an item have been established, even if it is rarely used, novel, or relatively unknown.[84] The statutory standard of "reasonable and necessary" has been translated by the HCFA into a need to show "safety and effectiveness."[85] The relation between a coverage decision by the HCFA and an approval decision by the FDA has not been well articulated, and a number of FDA-approved devices are not covered by Medicare.[82 , 85]

The issue of payment, which traditionally had been made under a cost-reimbursement system, involves how much the HCFA will reimburse the provider for both the cost of the device and the operating costs incurred in using the device. Medicare has traditionally reimbursed hospitals for the capital cost of a device on a cost-based, pass-through system. Medicare reimbursement for operating costs incurred by inpatient use of the device has become more complex since the adoption of the prospective payment system, which reimburses hospitals with a flat payment based on diagnosis-related groups.[86 87 88] Now, manufacturers must be sure that the procedures associated with their devices are placed in a diagnosis-related group that accurately reflects the operating costs, or be ready to argue for a change in the payment or for reclassification to another diagnosis-related group.

ANALYSIS OF THE REGULATORY PROCESS

Difficulties of Classification

The classification scheme was intended to provide a model regulatory framework. But after 11 years, important shortcomings are apparent. First, the process has proved to be unexpectedly time-consuming. Many pre-amendment devices have yet to be classified, despite original expectations that the process would take only a year. Detailed, congressionally mandated administrative procedures that the FDA is required to follow in classifying devices are largely responsible for the delays.[89 90 91 92 93 94 95 96]

The classification structure has also been undermined by the FDA's failure to issue performance standards for Class II devices.[5 , 10 , 24 , 33 , 64] Although more than 50 percent of 1700 devices will be assigned to Class II, not one performance standard has yet been issued. The requirement for performance standards is virtually the only distinction between Class II and Class I.[97] In the absence of performance standards, there are effectively two, rather than three, classes — one subject to premarketing approval (Class III) and one subject to compliance with general controls (Classes I and II).

Underreliance on Class I is also cited as a deficiency, especially by manufacturers.[98] Erring on the side of caution, the FDA has assigned nearly twice as many devices to Class II as to Class I. The general controls required of the devices in Class I can play an important part in ensuring safety and effectiveness, but complex administrative procedures that the FDA needs to follow in promulgating regulations, as well as politics, have delayed implementation of many of the controls. Only recently, for example, did the FDA implement mandatory reporting of adverse experiences, potentially one of the most valuable regulatory tools.[30]

The classification system is further hindered by the requirement that transitional devices automatically be assigned to Class III. Transitional devices include pre-amendment devices that

were regulated as drugs before 1976. By contrast, pre-amendment devices not regulated as drugs before 1976 are classified on the basis of risk. Transitional devices account for about 50 percent of all devices submitted for premarketing approval.[55] It would be a good idea to revise the statute to allow the FDA to classify (or reclassify) transitional devices on the basis of risk rather than previous regulatory status.

The problem that has most muddled the classification process is the statutory requirement that all new devices be assigned to Class III. This requirement would not be so troublesome if an efficient reclassification mechanism existed. Until recently, the FDA applied virtually the same criteria to reclassification decisions as it used in the premarketing-approval process.[99] Thus, in order to have a device reclassified, the manufacturer had to show that the device was safe and effective — a criterion that was even stricter than that for the initial classification.[100, 101] Recently, however, the FDA has shifted its position. Reclassification decisions are now based on whether the regulatory controls of the proposed new class adequately encompass the risks posed by the device.[14]

Although this change will make reclassification easier, the statute defines five types of reclassification, depending on the category of the device, and imposes different procedures for each reclassification. Uniform standards and procedures would unquestionably simplify the reclassification process.[99] Even more efficient would be a procedure that enabled the FDA to place each new device in Class I, II, or III, according to what it initially deems appropriate.

Lack of Performance Standards

The FDA's failure to develop performance standards has been attributed to the complex administrative rule-making procedures spelled out in the amendments and to the enormous extent of the undertaking.[102] Even if the process were simpler, the development of 800 performance standards for the 800 types of Class II devices, which has been estimated to require 50,000 staff years, would probably exceed the capability of the agency under any circumstances.[103, 104, 105]

Furthermore, performance standards have limited usefulness. First, rapid advances in medical technology can shorten their life span. Second, few devices are sufficiently alike, even within seemingly precise categories, to comply with a single standard. For example, there are several types of magnetic resonance imagers and several varieties of bone cement. Should a performance standard be written for each type? Who has the expertise to write such standards? What are the standards meant to accomplish?[106]

It has been suggested that a Class II-A be established. Devices assigned to this special category would be subject to more stringent controls than Class I devices; such controls might include increased reporting on devices and manufacturer-adopted performance standards to be reviewed by the FDA.[10] The agency has opposed this approach as too inflexible and duplicative of existing general controls.[107] Subdividing Class II devices would also require considerable resources, and it would probably be as time-consuming as the original classification process.[108]

An alternative is to reassign many Class II devices to Class I, another time-consuming and costly approach. It has also been proposed that Class II be eliminated altogether and that all Class II devices be assigned to Class I. Authority to develop and require performance standards could then be added to the general controls, thus preserving performance standards for specific uses.

The FDA has proposed that it be allowed to exercise its discretion in deciding whether performance standards are needed. Several years ago, the FDA identified 11 high-priority devices for which it intended to develop mandatory standards.[109] Recently, the FDA also offered limited funds to persons willing to propose standards for specific Class II devices.[105, 110] Congress should explicitly recognize that the FDA has made the development of performance standards discretionary and should streamline the complex procedures it has imposed on this process.

Premarketing Approval for Pre-Amendment Devices

The FDA has been harshly criticized for failing to require PMAs for pre-amendment devices.[5, 12] One possible approach to that problem is to assume that pre-amendment devices are safe and effective unless evidence indicates otherwise — that is, if a device has been used safely for a number of years, why require premarketing approval? [104] However, if premarketing-approval testing is not necessary, then the device should not have been assigned to Class III. Preamendment devices that have a substantial history of use with no important adverse experiences should be eligible for reclassification; an acceptable corollary would be to give the FDA discretion to focus on devices that have had serious adverse effects.

For pre-amendment devices that are appropriately assigned to Class III, the data required to demonstrate safety and effectiveness need not be the same as those necessary for new post-amendment Class III devices. For certain devices, abbreviated PMAs based on information about safety and effectiveness in the literature may be sufficient to meet the standard of "valid scientific evidence."

Overreliance on Findings of Substantial Equivalence

Widespread reliance on the 510(k) process raises a key question: How can the FDA determine that new substantially equivalent devices are safe and effective when comparable pre-amendment devices have not been proved to be so? Until the FDA requires premarketing testing of pre-

amendment devices or establishes performance standards for Class II devices, there will be a lack of data on the safety and effectiveness of post-amendment devices in the substantially equivalent category. Nevertheless, new devices will continue to receive approval under "equivalence creep" as 510(k)s build on 510(k)s, connected only by a thread of equivalence running through the succession of claims. Such piggybacking increases the number of generations of devices through which a claim of substantial equivalence may be demonstrated. As time passes and technology advances, it will become harder for device manufacturers to make successful claims of substantial equivalence for new and technologically different devices.[58]

Furthermore, how can the FDA limit substantial-equivalence findings to new devices whose new technological variations do not affect safety and effectiveness when the 510(k) process does not require the premarketing testing that ordinarily raises questions about those aspects of a device? Not surprisingly, to retain the administrative convenience of the 510(k) process while ensuring the safety and effectiveness of substantially equivalent devices, the FDA has sometimes required "mini-PMAs" or "hybrid 510(k)s," which must contain substantial data about the safety and effectiveness of a device, including information derived from clinical studies.[58 , 111] Although not specifically addressed by the amendments, the combining of the 510(k) and premarketing-approval processes is consistent with the amendments' goal of correlating regulatory effort with degree of risk. In any case, when confronted with the choice between submitting a PMA and complying with the FDA's hybrid 510(k) procedure, manufacturers are unlikely to object to the hybrid 510(k) requirements. The clinical data required by the FDA in hybrid 510(k)s are arguably limited to evidence of substantial equivalence. Theoretically, the evidence need only show that a new device performs as well as a similar pre-amendment device. In practice, the FDA does not limit its review to comparative performance, nor (from a public health perspective) should it do so, since the relevant issue is the degree of risk posed by the device, not its similarity to other devices.[111]

If the premarketing process is too cumbersome, at least for certain types of new devices, Congress should revise the law to require that the appropriate data on safety and effectiveness be included in an abbreviated PMA. Furthermore, the FDA's extensive reliance on the 510(k) pathway to reduce the number of devices that require premarketing approval — and consequently its own workload — is destined to fail. As technology advances, the number of devices legitimately found to be substantially equivalent to devices marketed before 1976 will diminish markedly. If the FDA does not soon develop other acceptable mechanisms for dealing with new devices, practical considerations will force it to stretch the statute further, making the regulation of medical devices even more perplexing.

Commercialization of Investigational Devices

The FDA has recently expressed concern about the widespread promotion and commercialization of investigational studies such as those involving the YAG laser, certain contact lenses, and intraocular lenses.[12 , 107] IDEs are often used to establish manufacturers' marketing positions for some expensive devices; this is especially important when a device will be a one-time purchase, and therefore, the market will quickly become saturated (Schroeher K: unpublished data). These issues arise because the FDA permits manufacturers to charge investigators for acquiring the investigational device; investigators may in turn pass the charges on to the subjects in their studies.[112] Under the cost-recovery provisions, patients may end up funding a considerable portion of the development of investigational devices. Manufacturers are not permitted, however, to commercialize investigational devices by charging more than the costs of manufacturing, researching, developing, and handling the device.[113] Whether manufacturers should be allowed to charge at all for devices whose safety and effectiveness have not been established is still open to question.

The amendments specifically require the agency to encourage the discovery and development of medical devices; they do not, however, specify whether manufacturers should be allowed to recover their costs — an option that may promote the discovery and development of devices. The offer of a free, unproved treatment can have undue influence on those who cannot afford to pay.[112] On the other hand, it is probably unwise to restrict participation in clinical trials of medical devices to those who can afford them.

Although the FDA does not get involved in cost accounting, it does monitor the number of subjects in each study, require the prompt submission of data, and require the termination of clinical trials if a device does not appear to be safe or effective. Furthermore, in some cases the agency has prevented holders of IDEs from expanding the scope of their investigations. Controlling the commercialization of devices that do not pose "significant" risks is difficult, however, because the FDA is rarely informed about studies of these products. For that reason, as well as to provide the option of monitoring certain investigations of devices that do not pose "significant" risks, it has been suggested that the agency be notified of all protocols for such investigations, possibly by means of an abbreviated IDE.[114]

FDA and HCFA Reviews

The HCFA's review of the safety and effectiveness of FDA-approved medical devices may seem redundant, given the FDA's mandate to ensure that new devices are safe and effective.[85 , 115 , 116] The HCFA insists that its review is different because the FDA's review is limited to whether the manufacturers' claims for its device are accurate. The HCFA claims that it must review the

effectiveness of the device as it is used by the medical community at large, focusing on the device's effectiveness in conventional practice settings. Some find that the HCFA's argument for a separate and distinct review of a device's safety and effectiveness is not compelling. The FDA does not approve a device for an abstract or theoretical purpose. Instead, each device is evaluated with reference to its intended uses, and it is usually approved for specifically defined clinical applications.

A substantial difference between the FDA and the HCFA reviews would exist if the HCFA required a formal cost-benefit or cost-effectiveness analysis before approval of the device. Some think that this requirement would provide the only rationale for a review by the HCFA. The HCFA, however, has been reluctant to admit that costs have a role in its decisions about whether to provide coverage. The part played by costs in decisions regarding Medicare coverage needs to be articulated.[82]

Changes in the Way Medicare Pays for Devices

The most striking change in the reimbursement of the costs of medical devices will be the reform of Medicare's capital payment policy.[117] [118] [119] [120] If, as currently proposed, capital expenditures are to be incorporated into the prospective payment system, the diffusion and availability of expensive medical devices may be dramatically affected. If adopted, the proposals would create even stronger incentives for hospitals to acquire technological equipment that reduces operating costs, rather than to enrich the services they offer. Even in the absence of changes in Medicare's capital payment policy, the prospective payment system creates incentives for hospitals to acquire cost-saving devices. Manufacturers are already shifting their emphasis from breakthrough technological equipment to cost-saving devices and from devices used in inpatient settings to those used in outpatient settings.[116] This shift will affect the development of important new medical devices. Although countervailing forces will continue to push for technological advances, Congress should cautiously assess any further changes in the way Medicare pays for medical devices.[88]

CONCLUSION

Congress should revise the Medical Device Amendments that were enacted in 1976. The basic principle of the amendments, that the degree of regulation imposed by the FDA should correlate with the degree of risk posed by a device, remains valid. However, the statute's innumerable mandatory regulatory requirements severely constrain administrative discretion. Although some observers, including some members of Congress, have been quick to criticize the FDA, it is more likely that the problems with implementation stem from the amendments themselves and are compounded by the limited resources the FDA has available for their implementation.

Fortunately, wholesale revision of laws regarding medical devices is not necessary. Rather, attention should be focused on several areas. First, findings of substantial equivalence should be limited to devices that are truly modern versions of pre-amendment devices. Second, new devices that are more than updated versions of pre-amendment devices but for which full premarketing testing is unnecessary should be subject to an abbreviated premarketing approval process. Third, the FDA's development of performance standards should be made discretionary, instead of being mandated, for all Class II devices, and it should focus on devices whose safety will be better ensured by the existence of such standards. Fourth, pre-amendment Class III devices that do not require extensive testing should either be reassigned to Class I or II or be exempted, on the basis of their safety records, from premarketing approval. Fifth, automatic assignment of new devices, especially transitional devices, to Class III should be reconsidered. Sixth, an effective reclassification procedure should be instituted. Some of these changes require legislative revision; others can be accomplished administratively.

Furthermore, the medical community needs to have a better understanding of its responsibilities under the Medical Device Amendments: institutional review boards need to understand the regulations regarding IDEs; sponsors need to understand the content, formats, and rules governing 510(k)s, PMAs, and IDEs; and physicians need to understand the rules that govern investigational, emergency, and unapproved uses of medical devices.

Recognition of the extraordinary effect of federal reimbursement policies on the development of medical devices is as important as revision of the FDA approval process. The necessity for a separate coverage decision by the HCFA, based on a device's safety and effectiveness — the same statutory standard employed by the FDA — must be examined. If the standards used by the two agencies differ, the differences should be articulated. At the very least, the approval of devices that reflect breakthroughs in technology and have the potential to affect medical care should not be subject to unnecessary delays.

Ultimately, the willingness of third-party payers to reimburse health care providers for costs associated with the use of a device will have the greatest effect on the development of new devices. The method by which capital investment is reimbursed and payment levels are assigned to each diagnosis-related group will profoundly affect the development and availability of new devices.

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SOURCE INFORMATION

From the Jack D. Weiler Hospital of the Albert Einstein College of Medicine, Bronx, N.Y., and Patton, Boggs, and Blow, Washington, D.C. Dr. Sundwall's contribution was based on his work while with the United States Senate Committee on Labor and Human Resources, Address reprint requests to Dr. Kessler at the Jack D. Weiler Hospital of the Albert Einstein College of Medicine, 1825 East-chester Rd., Bronx, NY 10461.

EXHIBIT K

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 39 Footnotes 21 & 22

FDA U.S. FOOD & DRUG ADMINISTRATION

522 Postmarket Surveillance Studies

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522 Order Number[7][8]	Manufacturer[9][10]	Device Name[11][12]	Medical Specialty	Date 522 Order[13][14]	Study Name	Study Status
PS160003	Parker Hannifin Corporation	Indego	Physical Medicine	04/15/2016	Indego Postmarket Surveillance Study[15]	Progress Adequate
PS160001	Bayer Healthcare, LLC	Essure system for permanent birth control	Obstetrics/ Gynecology	02/29/2016	Postmarket Surveillance Study[16]	Progress Adequate
PS150004	Pentax Medical	Duodenoscopes	Gastroenterology/ Urology	10/05/2015	Human Factors Study[17]	Plan Pending
					Sampling and Culturing Study[18]	Progress Inadequate
PS150003	Olympus Medical Systems Corporation (OMSC.	Duodenoscopes	Gastroenterology/ Urology	10/05/2015	Human Factors Study[19]	Plan Pending
					Sampling and Culturing Study[20]	Progress Inadequate
PS150002	Fujifilm Medical Systems USA, Inc.	Fujifilm duodenoscopes	Gastroenterology/ Urology	10/05/2015	Human Factors Study[21]	Plan Pending
					Sampling and Culturing Study[22]	Progress Inadequate
PS150001	Preceptis	Hummingbird tympanostomy tube system	Ear Nose & Throat	04/23/2015	Post-market Surveillance Study (PSS) [23]	Progress Adequate
PS140004	Genzyme Sanofi	GlucaMesh and Glucatex (Polypropylene/Polyester) Mesh	General & Plastic Surgery	12/11/2014	PSS[24]	Other
PS140002	Bard Peripheral Perivascular	Simon Nitinol System	Cardiovascular	10/17/2014	Simon Nitinol PS[25]	Other
PS140001	Argo Medical Technologies, Inc	Rewalk	Physical Medicine	06/26/2014	ReWalk Registry[26]	Progress Inadequate
PS130047	Herniamesh SRL	T-Sling	Obstetrics/ Gynecology	09/26/2013	PSS[27]	Terminated
PS130046	St. Jude Medical, Inc.	Amplatzer	Cardiovascular	09/30/2013	ADVANCE ASO[28]	Progress Adequate
PS130045	Aesculap, Inc.	Modular range of ring pros. For hip replacement	Orthopedic	07/29/2013	PSS[29]	Terminated
PS130044	Boston Scientific Corporation	Pinnacle LITE Pelvic Floor Repair Kits - Uphold Lite Posterior and Uphold	Obstetrics/ Gynecology	07/03/2013	POP AE and Effectiveness rates, registry[30]	Progress Inadequate
					Posterior Lite[31]	Other
PS130043	Aesculap, Inc.	Ring upm total hip replacement	Orthopedic	07/29/2013	PSS[32]	Terminated
PS130042	Baxter Healthcare Corp	Vena Cava Filter	Cardiovascular	07/29/2013	PSS[33]	Other
PS130041	Halt Medical Inc.	Acessa system	Obstetrics/ Gynecology	06/17/2013	Newly Enrolled[34]	Progress Adequate
					(IDE) Long Term Follow-up[35]	Completed
PS130040	Cook Biotech Inc.	Biodesign® Surgisis® Anterior and Posterior Pelvic Floor Grafts	Obstetrics/ Gynecology	06/17/2013	AE and Effectiveness Rates[36]	Other

PS130039	Coloplast Corp	Altis single incision sling system	Obstetrics/ Gynecology	03/13/2013	AE and effectiveness rates[37]	Progress Adequate
PS130038	C.R. Bard Inc.	Ajust helical adjustable single-incision sling	Obstetrics/ Gynecology	03/13/2013	PSS[38]	Other
PS130037	American Medical Systems, Inc.	Miniarc pro single-incision sling system	Obstetrics/ Gynecology	03/13/2013	PSS[39]	Consolidated
PS130036	RTI Biologics, Inc.	Tutopatch	General & Plastic Surgery	03/13/2013	PSS[40]	Terminated
PS130035	TFS Surgical	Tissue fixation system	General & Plastic Surgery	05/15/2013	AE and Effectiveness Rates[41]	Other
PS130034	Prosurg, Inc.	Surgical mesh w/anchoring system	General & Plastic Surgery	03/13/2013	PSS[42]	Other
PS130033	Prosurg, Inc.	Zippere- bioabsorbable/non-absorbable polymer sling & surgical mesh	General & Plastic Surgery	03/13/2013	AE and Effectiveness Rates[43]	Other
PS130032	Organogenesis, Inc.	FortaPerm surgical sling	General & Plastic Surgery	03/13/2013	PSS[44]	Other
PS130031	Organogenesis, Inc.	Fortaflex surgical sling	General & Plastic Surgery	03/13/2013	PSS[45]	Other
PS130030	Coloplast Corp	Mentor suspend sling	General & Plastic Surgery	03/13/2013	PSS[46]	Other
PS130029	Covidien	Ivs tunneller devices	General & Plastic Surgery	03/13/2013	PSS[47]	Other
PS130028	Covidien	Ivs tunneller	Neurology	03/13/2013	PSS[48]	Other
PS130027	Caldera Medical Inc.	Desara mesh	Obstetrics/ Gynecology	03/13/2013	PSS[49]	Terminated
PS130026	Caldera Medical Inc.	Desara mesh	Obstetrics/ Gynecology	03/13/2013	PSS[50]	Terminated
PS130025	Caldera Medical Inc.	Desara mesh sling, model cal-dsol	Obstetrics/ Gynecology	03/13/2013	PSS[51]	Terminated
PS130024	Caldera Medical Inc.	Caldera mesh	General & Plastic Surgery	03/13/2013	PSS[52]	Other
PS130023	Caldera Medical Inc.	T-sling	Obstetrics/ Gynecology	03/13/2013	PSS[53]	Terminated
PS130022	Boston Scientific Corporation	Modification to Surgical Mesh Polymeric	Obstetrics/ Gynecology	03/13/2013	PSS[54]	Terminated
PS130021	Boston Scientific Corporation	Modification to trelex mesh surgical mesh	Obstetrics/ Gynecology	03/13/2013	PSS[55]	Terminated
PS130020	Boston Scientific Corporation	Surgical fabrics	General & Plastic Surgery	03/13/2013	PSS[56]	Other
PS130019	American Medical Systems, Inc.	Pfr sling system, (part of the pelvic floor repair system)	General & Plastic Surgery	03/13/2013	PSS[57]	Other
PS130018	American Medical Systems, Inc.	Topas system	General & Plastic Surgery	03/13/2013	PSS[58]	Other
PS130017	American Medical Systems, Inc.	Ams triangle silicone-coated sling and surgical mesh	General & Plastic Surgery	03/13/2013	PSS[59]	Other
PS130016	Promedon	Ophira mini sling system	Obstetrics/ Gynecology	03/13/2013	PSS[60]	Terminated
PS130015	DIMA	Contasure Needleless sling	General & Plastic Surgery	03/13/2013	AE and Effectiveness Rates[61]	Completed
PS130013	Herniamesh SRL	Hemiamesh t-sling	General & Plastic Surgery	03/13/2013	PSS[62]	Terminated
PS130012	Coloplast Corp	Mentor suspend sling	General & Plastic Surgery	03/13/2013	PSS[63]	Other
PS130011	American Medical Systems, Inc.	Elevate prolapse repair systems	Obstetrics/ Gynecology	03/13/2013	AE & Effectiveness Rates[64]	Consolidated
PS130010	MicroPort	Link metal-backed acetabular cups	Orthopedic	03/20/2013	PSS[65]	Terminated
PS130009	Wright Medical Technology, Inc.	Linked metal-backed acetabular cups	Orthopedic	03/20/2013	PSS[66]	Other
PS130008	Rmt Medical Technologies Ltd	Vena cava filter	Cardiovascular	02/28/2013	PSS[67]	Other
PS130005	Cook Incorporated	Vena Cava Filter	Cardiovascular	02/28/2013	PSS[68]	Other
PS130002	Boston Scientific Corporation	Vena cava filters	Cardiovascular	02/28/2013	Greenfield PS study[69]	Completed
PS130001	Boston Scientific Corporation	Greenfield vena cava filters	Cardiovascular	02/28/2013	Greenfield PS study[70]	Completed
PS120111	St. Jude Medical, Inc.	Riata, quicksite, quickflex, durata	Cardiovascular	08/16/2012	Lead Externalization and Abrasion[71]	Progress Adequate
PS120110	Stryker Neurovascular	Wingspan stent system and gateway pta balloon catheter	Neurology	08/08/2012	Rates of Stroke and Death[72]	Progress Adequate
PS120109	Cook Biotech Inc.	Surgisis sling	Obstetrics/ Gynecology	04/09/2012	AE & Effectiveness Rates[73]	Terminated
					J-PF-POST, J-SLH, J-PFV, J-PF and J-PF-ANT models[74]	Terminated
PS120108	Tepha, Inc.	Tephaflex composite mesh	General & Plastic Surgery	04/09/2012	AE & Effectiveness Rates[75]	Terminated
PS120107	Tepha, Inc.	Tephaflex surgical film	General & Plastic Surgery	04/09/2012	AE & Effectivenss Rates[76]	Terminated
PS120106	Coloplast Corp.	Restorelle polypropylene mesh	Obstetrics/	04/09/2012	POP AE and	Progress Adequate

			Gynecology		Effectiveness rates, registry[77] Restorelle P, EZA, EZP, and L models[78]	Other
PS120105	Herniamesh SRL	T-sling	Obstetrics/ Gynecology	04/09/2012	AE & Effectiveness Rates[79]	Other
PS120104	Herniamesh SRL	Biosling Bioabsorbable Polymer Sling & Surgical Mesh	General & Plastic Surgery	04/09/2012	AE & Effectiveness Rates[80]	Terminated
PS120103	Injectx, Inc	Biosling bioabsorbable polymer sling & surgical mesh	General & Plastic Surgery	04/09/2012	PSS[81]	Other
PS120102	Caldera Medical Inc.	Desara mini	Obstetrics/ Gynecology	04/09/2012	AE & Effectiveness Rates[82]	Other
PS120101	IBI Israel Biomedical Innovations	Endofast reliant¿.	General & Plastic Surgery	04/09/2012	AE & Effectiveness Rates[83]	Other
PS120100	IBI Israel Biomedical Innovations	EndoFast Reliant¿.	General & Plastic Surgery	04/09/2012	AE and Effectiveness Rates[84]	Other
PS120099	Prosurg, Inc.	Minisling adjustable polymer sling & surgical mesh with self-anchoring system (easy lift prolapse repair & minisling)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[85]	Other
PS120098	Coloplast Corp	Minitape urethral sling	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[86]	Other
PS120097	Coloplast Corp	Minitape urethral sling	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[87]	Other
PS120096	Coloplast Corp	Gyne ideas minitape rp device	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[88]	Other
PS120095	Ethicon, Inc.	Gynecare tvt secur system	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[89]	Other
PS120094	C.R. Bard Inc.	Ajust adjustable single incision sling	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[90]	Other
PS120093	Boston Scientific Corporation	Solyx Single Incision Sling System	General & Plastic Surgery	01/03/2012	SUI AE and Effectiveness rates[91]	Progress Adequate
PS120092	American Medical Systems, Inc.	Miniarc precise single-incision sling system	General & Plastic Surgery	01/03/2012	SUI AE and Effectiveness rates[92]	Consolidated
PS120091	American Medical Systems, Inc.	Miniarc precise single-incision sling system	General & Plastic Surgery	01/03/2012	SUI AE and Effectiveness rates[93]	Consolidated
PS120090	American Medical Systems, Inc.	Miniarc precise single-incision sling system	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[94]	Other
PS120089	Astora Womens Health	Miniarc precise single-incision sling system	General & Plastic Surgery	01/03/2012	SUI AE and Effectiveness rates[95]	Other
PS120088	Xylos Corporation	Xylos porous surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[96]	Other
PS120087	Xylos Corporation	Xylos porous surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[97]	Other
PS120086	W.L. Gore & Associates, Inc.	Seamguard staple line reinforcement material	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[98]	Terminated
PS120085	W.L. Gore & Associates, Inc.	Gore bioabsorbable mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[99]	Terminated
PS120084	W.L. Gore & Associates, Inc.	Modification to seamguard staple line reinforcement material	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[100]	Terminated
PS120083	W.L. Gore & Associates, Inc.	Seamguard staple line reinforcement material	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[101]	Terminated
PS120082	Tei Biosciences Inc.	Xenform soft tissue repair matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[102]	Other
PS120081	Boston Scientific	Xenform soft tissue repair matrix	General & Plastic Surgery	01/03/2012	POP AE and Effectiveness rates, registry[103]	Progress Adequate
PS120080	Tei Biosciences Inc.	Tissuemend soft tissue repair matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[104]	Other
PS120079	Tepha, Inc.	Tephaflex surgical mesh	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[105]	Terminated
PS120078	Synovis Surgical Innovations	Veritas collagen matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[106]	Terminated

PS120077	Synovis Surgical Innovations	Veritas collagen matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[107]	Terminated
PS120076	Covidien	Permacol surgical implant t-piece permacol surgical implant rectocele-piece models 5928-150 5645-150; Permacol surgical implant	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[108]	Other
PS120075	Covidien	Permacol surgical implant t-piece permacol surgical implant rectocele-piece models 5928-150 5645-150	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[109]	Other
PS120074	Sofradim Production	Parietex	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[110]	Terminated
PS120073	Sofradim Production	Ugytex mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[111]	Other
PS120072	Covidien	Ugytex dual knit mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[112]	Other
PS120071	Covidien	Parietene duo and quadra polypropylene meshes	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[113]	Other
PS120070	Shelhigh, Inc.	SHELHIGH NO-REACT TISSUE REPAIR PATCH/UROPATCH.	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[114]	Terminated
PS120069	Shelhigh, Inc.	Shelhigh porcine pericardial patch	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[115]	Terminated
PS120068	RTI Biologics, Inc.	Tutopatch tutomesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[116]	Other
PS120067	Proxy Biomedical Ltd.	Polyform synthetic mesh	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[117]	Terminated
PS120066	Promethean Surgical Devices, Inc.	Hydrocoat mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[118]	Other
PS120065	Synovis Surgical Innovations	Orthadapt pr; Orthadapt bioimplant; Pegasus biologics orthadapt surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[119]	Terminated
PS120064	Synovis Surgical Innovation	Orthadapt pr; Orthadapt bioimplant; Pegasus biologics orthadapt surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[120]	Terminated
PS120063	Synovis Surgical Innovation	Orthadapt pr; Orthadapt bioimplant; Pegasus biologics orthadapt surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[121]	Terminated
PS120062	Smith & Nephew	Immix thin film models: Pss-004-s pss-004-sp pss-004-m pss-004-mp pss-004-l pss-004-lp	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[122]	Other
PS120061	Smith & Nephew, Inc	Immix plastifilm	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[123]	Other
PS120060	Organogenesis, Inc.	FORTAFLEX SURGICAL MESH	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[124]	Other
PS120059	Organogenesis, Inc.	FORTAFLEX SURGICAL MESH	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[125]	Other
PS120058	Organogenesis, Inc.	FORTAFLEX SURGICAL MESH	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[126]	Other
PS120057	Neomedic International	SURELIFT PROLAPSE SYSTEM	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[127]	Other
PS120056	Coloplast Corp	Minimesh polypropylene mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[128]	Other
					Restorelle P, EZA and L models[129]	Other
PS120055	Coloplast Corp	Minimesh polypropylene mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[130]	Other
					Restorelle P, EZA and L model[131]	Other
PS120053	Herniamesh SRL	Pelvimesh / hermesh 7	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[132]	Other
PS120052	Cytori Therapeutics, Inc.	Macropore surgiwrap (ts)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[133]	Other
PS120051	DSM Biomedical	Kensey nash ecm surgical patch	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[134]	Terminated
PS120050	DSM Biomedical	Medeor matrix models 30010-xx (hydrated); 30020-xx (dry)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[135]	Terminated
PS120049	DSM Biomedical	Bioblanket surgical mesh	General &	01/03/2012	AE and	Other

			Plastic Surgery		effectiveness rates[136]	
PS120048	DSM Biomedical	Bioblanket surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[137]	Other
PS120047	PFM Medical	Timesh also known as timesh-tc models 6000001 & 6000004	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[138]	Terminated
PS120046	Ethicon, Inc.	Gynemesh prolene soft (polypropylene) nonabsorbable synthetic surgical mesh for pelvic floor repair	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[139]	Other
PS120045	Ethicon, Inc.	Tbd ethicon mesh (gynecare gynemesh m)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[140]	Other
PS120044	Ethicon, Inc.	Gynecare prosima pelvic floor repair systems	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[141]	Other
PS120043	Ethicon, Inc.	Gynecare prolift +m* pelvic floor repair systems	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[142]	Other
PS120042	CryoLife, Inc.	Propatch soft tissue repair matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[143]	Terminated
PS120041	CryoLife, Inc.	Propatch soft tissue repair matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[144]	Terminated
PS120040	Cousin Biotech SARL	Biotech SAS for Biomesh® PI and Biomesh® Plug and Patch	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[145]	Terminated
PS120039	Cook Biotech Inc.	Surgisis staple line reinforcement	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[146]	Other
PS120038	Coloplast Corp	Restorelle polypropylene mesh; Restorelle polypropylene mesh	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[147]	Other
					Restorelle P, EZA, EZP, and L models[148]	Other
PS120037	Coloplast Corp	Mentor novasilk mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[149]	Other
PS120036	Coloplast Corp	Exair anterior and posterior prolapse repair systems	Obstetrics/ Gynecology	01/03/2012	POP AE and Effectiveness rates, registry[150]	Consolidated
PS120035	Coloplast Corp	Exair anterior and posterior prolapse repair systems	General & Plastic Surgery	01/03/2012	POP AE and Effectiveness rates, registry[151]	Other
PS120034	Caldera Medical Inc.	Ascend blue ac mesh; Ascend blue pc mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[152]	Other
PS120033	Caldera Medical Inc.	Ascend blue ac mesh; Ascend blue pc mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[153]	Other
PS120032	Caldera Medical Inc.	Popmesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates-PoP Mesh[154]	Other
PS120031	C.R. Bard Inc.	Bard pelvisoft acellular collagen biomesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[155]	Other
PS120030	C.R. Bard Inc.	Bard prolapse repair system	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[156]	Terminated
PS120029	C.R. Bard Inc.	Avaulta solo synthetic support system avaulta plus biosynthetic support system; Avaulta support system	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[157]	Other
PS120028	C.R. Bard Inc.	Avaulta solo synthetic support system avaulta plus biosynthetic support system; Avaulta support system	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[158]	Other
PS120027	C.R. Bard Inc.	Avaulta solo synthetic support system avaulta plus biosynthetic support system; Avaulta support system	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[159]	Other
PS120026	Stellen Medical	Dermmatrix surgical mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[160]	Other
PS120025	Stellen Medical	Brennen medical surgical mesh glucamesh/glucatex	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[161]	Other
PS120024	Boston Scientific Corporation	Pinnacle pelvic floor repair kits (pinnacle)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates-Anterior[162]	Other
					Posterior[163]	Other
PS120023	Boston Scientific Corporation	Pinnacle pelvic floor repair kit ii (uphold)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates-Uphold[164]	Other
PS120022	Boston Scientific Corporation	Pelvic floor repair system (pinnacle duet)	General & Plastic Surgery	01/03/2012	AE and effectiveness rates-Duet[165]	Other

PS120021	Boston Scientific Corporation	Lite pelvic floor repair kits	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates for Uphold LITE[166]	Other
					DUET LITE[167]	Other
					Posterior LITE[168]	Other
					Anterior LITE[169]	Other
PS120020	Synovis Surgical Innovations / Baxter	Supple peri-guard pericardium	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[170]	Terminated
PS120019	Synovis Surgical Innovations / Baxter	Peri-guard pericardium	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[171]	Terminated
PS120018	Synovis Surgical Innovations / Baxter	Supple peri-guard pericardium	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[172]	Terminated
PS120017	Synovis Surgical Innovations	Peri-strips	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[173]	Other
PS120016	Synovis Surgical Innovations / Baxter	Peri-guard cv peri-guard ocu-guard supple peri-guard peri-strips - sleeve peri-strips-strips peri-strips dry vasc	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[174]	Terminated
PS120015	American Medical Systems, Inc.	Ams collagen dermal matrix, ams apogee system with pre-connected collagen dermal matrix, ams perigee system with pre-connected collagen dermal matrix	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[175]	Other
PS120014	American Medical Systems, Inc.	Elevate prolapse repair system with pc coated intepro lite- apical and posterior prolapse repair system anterior and ap	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[176]	Other
PS120013	American Medical Systems, Inc.	Apogee and perigee systems with pc coated intepro lite	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[177]	Other
PS120012	American Medical Systems, Inc.	Apogee and perigee systems with intepro lite and intexen lp part of the ams pelvic floor repair system; Ams collagen dermal matrix, ams apogee system with pre-connected collagen dermal matrix, ams perigee system with pre-connected collagen dermal matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[178]	Other
PS120011	American Medical Systems, Inc.	Apogee and perigee systems with intepro lite and intexen lp part of the ams pelvic floor repair system; Ams collagen dermal matrix, ams apogee system with pre-connected collagen dermal matrix, ams perigee system with pre-connected collagen dermal matrix	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[179]	Other
PS120010	American Medical Systems, Inc.	Apogee and perigee systems with intepro lite and intexen lp part of the ams pelvic floor repair system; Ams collagen dermal matrix, ams apogee system with pre-connected collagen dermal matrix, ams perigee system with pre-connected collagen dermal matrix	General & Plastic Surgery	01/03/2012	Apogee AE and Eff Rates[180]	Other
					Perigee AE and Eff Rates[181]	Other
PS120009	American Medical Systems, Inc.	Apogee and perigee systems with intepro lite and intexen lp part of the ams pelvic floor repair system; Ams collagen dermal matrix, ams apogee system with pre-connected collagen dermal matrix, ams perigee system with pre-connected collagen dermal matrix	General & Plastic Surgery	01/03/2012	Apogee and Perigee System w/IntePro Lite[182]	Other
PS120008	American Medical Systems, Inc.	Ams elevate apical and posterior prolapse repair system with intepro lite or intexen lp	Obstetrics/ Gynecology	01/03/2012	AE and Effectiveness Rates[183]	Other
PS120007	American Medical Systems, Inc.	Ams elevate apical and posterior prolapse repair system with intepro lite or intexen lp	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[184]	Other
PS120006	Astora Womens Health	Ams elevate apical and posterior prolapse repair system with intepro lite	General & Plastic Surgery	01/03/2012	POP AE and Effectiveness rates, registry[185]	Other
					Elevate System w/InteXen LP[186]	Other
PS120005	American Medical Systems, Inc.	Ams elevate anterior & apical prolapse repair system with intepro lite	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[187]	Other
PS120004	Astora Womens Health	Ams elevate anterior & apical prolapse repair system with intepro llite	General & Plastic Surgery	01/03/2012	POP AE and effectiveness rates, registry[188]	Other
PS120003	American Medical Systems, Inc.	Ams large pore polypropylene mesh	General & Plastic Surgery	01/03/2012	AE and effectiveness rates[189]	Other
PS120002	American Medical Systems, Inc.	Ams large pore polypropylene mesh	Obstetrics/ Gynecology	01/03/2012	AE and effectiveness rates[190]	Other
PS120001	Acell, Inc.	Acell matristem pelvic floor matrix	General & Plastic Surgery	01/03/2012	POP AE and Effectiveness rates, registry[191]	Progress Adequate
PS110149	Depuy Orthopaedics, Inc.	Depuy corail hip system, revision stem	Orthopedic	05/06/2011	PSS[192]	Terminated
PS110148	MicroPort	Conserve bio foam shell	Orthopedic	05/06/2011	Metal ion levels[193]	Consolidated
PS110147	Turnkey Intergration USA, Inc.	Modified freeman revision acetabular cup	Orthopedic	05/06/2011	Metal ion levels[194]	Terminated
PS110146	Turnkey Intergration USA, Inc.	Modified freeman acetabular cup	Orthopedic	05/06/2011	Metal ion levels[195]	Terminated
PS110145	Techmedica, Inc.	TECHMEDICA MUELLER TYPE POLYETHYLENE ACETBUL CUP	Orthopedic	05/06/2011	Metal ion levels[196]	Terminated
PS110144	Synergy Orthopaedics Intl., Inc.	S.A.F. Acetabular cup	Orthopedic	05/06/2011	Metal ion levels[197]	Terminated
PS110142	Osteotechnology, Inc.	Thompson type hip prothesis	Orthopedic	05/06/2011	Metal ion levels[198]	Terminated
PS110141	Osteotechnology, Inc.	Biometric screw fixation cup	Orthopedic	05/06/2011	PSS[199]	Terminated

PS110140	Orthopaedic Device Corp.	P.T.H. METAL-BACKED ACETABULAR CUP	Orthopedic	05/06/2011	Metal ion levels[200]	Terminated
PS110139	Med-Tek Corp.	H.N. Metal backed acetabular cup, noncemented	Orthopedic	05/06/2011	Metal ion levels[201]	Terminated
PS110138	Joint Medical Products Corp.	S-ROM(R) ZTT(TM) ACETABULAR CUP-APICAL HOLE PLUG	Orthopedic	05/06/2011	Metal Ion Levels[202]	Terminated
PS110137	Joint Medical Products Corp.	S-ROM ACETABULAR CUP(PART OF S-ROM 135TM TOTAL HIP	Orthopedic	05/06/2011	Metal ion levels[203]	Terminated
PS110136	Implantology LLC	Fpc/sfpc/rfpc acetabular component	Orthopedic	05/06/2011	Metal ion levels[204]	Other
PS110135	Implantology LLC	Cps acetabular component	Orthopedic	05/06/2011	Metal ion levels[205]	Other
PS110134	Endomedics, Inc.	SELF-ALIGNING ACETABULAR COMPONENT	Orthopedic	05/06/2011	Metal ion levels[206]	Terminated
PS110133	Downs Surgical Ltd.	MODULAR RANGE OF RING PROS. FOR HIP REPLACEMENT	Orthopedic	05/06/2011	Metal ion levels[207]	Terminated
PS110132	Downs Surgical Ltd.	RING UPM TOTAL HIP REPLACEMENT	Orthopedic	05/06/2011	Metal ion levels[208]	Terminated
PS110131	C.R. Bard Inc.	CONTOUR II LINK SP TOTAL HIP PROSTHESIS	Orthopedic	05/06/2011	Metal ion levels[209]	Terminated
PS110130	American Ortomed Corp.	Uniloc-cementless & self tap acetabular	Orthopedic	05/06/2011	Metal ion levels[210]	Terminated
PS110129	American Ortomed Corp.	Titanium mittelmeier type acetabular	Orthopedic	05/06/2011	Metal ion levels[211]	Terminated
PS110128	Advanced Bioresearch Association	Freeman acetabular cup	Orthopedic	05/06/2011	Metal ion levels[212]	Terminated
PS110127	Advanced Bioresearch Association	Weill cementless threaded acetabular cup	Orthopedic	05/06/2011	Metal ion levels[213]	Terminated
PS110126	Advanced Bioresearch Association	Pm cementless screw-in acetabular cup	Orthopedic	05/06/2011	Metal ion levels[214]	Terminated
PS110125	Advanced Bioresearch Association	Muller titanium backed acetabular cup component	Orthopedic	05/06/2011	Metal ion levels[215]	Terminated
PS110124	Advanced Bioresearch Association	Natural lock acetabular component	Orthopedic	05/06/2011	Metal ion levels[216]	Terminated
PS110123	Orthopedic Manufacturing Co.	Ace 100 degrees tubular plate	Orthopedic	05/06/2011	Metal ion levels[217]	Terminated
PS110122	Waldemar Link GMBH & Co. KG	Link cementless screw-in acetabular cup	Orthopedic	05/06/2011	Metal ion levels[218]	Terminated
PS110121	Waldemar Link GMBH & Co. KG	Link cementless screw-in acetabular cup	Orthopedic	05/06/2011	Metal ion levels[219]	Terminated
PS110120	Link America, Inc.	Link metal-backed acetabular cups	Orthopedic	05/06/2011	Metal ion levels[220]	Terminated
PS110119	Link America, Inc.	Lidgrer-lund acetabular sockets	Orthopedic	05/06/2011	Metal ion levels[221]	Terminated
PS110118	Zimmer	Zimmer m/l taper hip prosthesis with kinectiv technology system	Orthopedic	05/06/2011	Cross-sectional Plan[222]	Consolidated
					Prospective Study Plan[223]	Terminated
PS110117	Zimmer	Versys epoch fullcoat hip prosthesis, model 4088 series	Orthopedic	05/06/2011	Metal ion levels[224]	Consolidated
PS110116	Zimmer	Zimmer m/l taper hip prosthesis with kinectiv technology system, model(s) 7848 series (modular necks), 7713 series	Orthopedic	05/06/2011	Cross-sectional Plan[225]	Consolidated
					Prospective Study Plan[226]	Terminated
PS110115	Zimmer	Zimmer m/l taper hip prosthesis with modular neck technology	Orthopedic	05/06/2011	Cross-sectional Plan[227]	Consolidated
					Prospective Study Plan[228]	Terminated
PS110114	Zimmer	Zimmer threaded acetabular cup	Orthopedic	05/06/2011	Metal ion levels[229]	Terminated
PS110113	Zimmer	Metasul taper liners, metasul femoral heads	Orthopedic	05/06/2011	Cross-sectional Plan[230]	Consolidated
					Prospective Study plan[231]	Terminated
PS110112	Zimmer	Zimmer mmc cup	Orthopedic	05/06/2011	Metal ion levels[232]	Consolidated
PS110111	Zimmer	Zimmer porolock mis stem	Orthopedic	05/06/2011	Metal ion levels[233]	Consolidated
PS110110	Zimmer	Durom acetabular component and metasul ldh large diameter heads	Orthopedic	05/06/2011	Metal ion levels[234]	Consolidated
PS110109	Zimmer	Ascendent acetabular system	Orthopedic	05/06/2011	Metal ion levels[235]	Other
PS110108	Zimmer	Allofit acetabular system	Orthopedic	05/06/2011	Metal ion levels[236]	Consolidated
PS110107	Zimmer	Inter-op metasul hooded and protrusio acetabular inserts	Orthopedic	05/06/2011	Metal ion levels[237]	Other
PS110106	Zimmer	Inter-op metasul acetabular system	Orthopedic	05/06/2011	Metal ion levels[238]	Consolidated
PS110105	Zimmer	Apr metasul acetabular insert	Orthopedic	05/06/2011	Metal ion levels[239]	Other
PS110102	Zimmer	Clx acetabular cup (wagner) for cementless fixation	Orthopedic	05/06/2011	Metal ion levels[240]	Terminated
PS110101	Zimmer	Schuster acetabular cup for cement/cementless fix	Orthopedic	05/06/2011	Metal ion levels[241]	Terminated
PS110100	Zimmer	Modified anatomic porous replacement apr acetabula	Orthopedic	05/06/2011	Metal ion levels[242]	Terminated
PS110098	Zimmer	Alpha metasul 28mm and 32mm acetabular inserts, standard and hooded	Orthopedic	05/06/2011	Metal ion	Consolidated

					levels[243]	
PS110097	Zimmer	Epsilon metasul 32mm acetabular inserts, standard and hooded	Orthopedic	05/06/2011	Metal ion levels[244]	Consolidated
PS110096	Zimmer	Converge reti-lock multi-hole reinforcement cup	Orthopedic	05/06/2011	Metal ion levels[245]	Consolidated
PS110094	Zimmer	Rs-cup acetabular prosthesis	Orthopedic	05/06/2011	Metal ion levels[246]	Terminated
PS110093	Zimmer	Zweymueller-sl hip prosthesis stem	Orthopedic	05/06/2011	Cross-Sectional Study[247]	Progress Inadequate
					Explant Analysis[248]	Progress Adequate
PS110092	Zimmer	Zweymuller cup	Orthopedic	05/06/2011	Metal ion levels[249]	Terminated
PS110091	MicroPort	Profemur hip system modular necks	Orthopedic	05/06/2011	Metal ion levels[250]	Consolidated
PS110090	MicroPort	Dynasty porous acetabular shell, dynasty polyethylene acetabular liner, dynasty metal acetabular liner	Orthopedic	05/06/2011	Metal ion levels[251]	Consolidated
PS110089	MicroPort	Profemur lx 5/8 coated hip stem	Orthopedic	05/06/2011	Metal ion levels[252]	Consolidated
PS110088	MicroPort	Profemur lx revision 5/8 coated hip stem	Orthopedic	05/06/2011	Metal ion levels[253]	Consolidated
PS110087	MicroPort	Dynasty acetabular system	Orthopedic	05/06/2011	Metal ion levels[254]	Consolidated
PS110086	MicroPort	Dynasty acetabular shell and cocr acetabular liner	Orthopedic	05/06/2011	Metal ion levels[255]	Consolidated
PS110085	MicroPort	Profemur tl hip stem	Orthopedic	05/06/2011	Metal ion levels[256]	Consolidated
PS110084	MicroPort	Conserve plus quadrafix acetabular shell	Orthopedic	05/06/2011	Metal ion levels[257]	Consolidated
PS110083	MicroPort	Profemur lx hip stem	Orthopedic	05/06/2011	Metal ion levels[258]	Consolidated
PS110082	MicroPort	Profemur xtr hip stem	Orthopedic	05/06/2011	Metal ion levels[259]	Consolidated
PS110081	MicroPort	Conserve total femoral head	Orthopedic	05/06/2011	Metal ion levels[260]	Consolidated
PS110080	MicroPort	Profemur renaissance hip stem	Orthopedic	05/06/2011	Metal ion levels[261]	Consolidated
PS110079	MicroPort	Conserve plus ha acetabular shells	Orthopedic	05/06/2011	Metal ion levels[262]	Consolidated
PS110078	MicroPort	Lineage ha acetabular shells	Orthopedic	05/06/2011	Metal ion levels[263]	Consolidated
PS110077	MicroPort	Procotyl-e acetabular system	Orthopedic	05/06/2011	Metal ion levels[264]	Consolidated
PS110076	MicroPort	Profemur tapered hip stem	Orthopedic	05/06/2011	Metal ion levels[265]	Consolidated
PS110075	MicroPort	Conserve plus revision shell and conserve plus thick shell	Orthopedic	05/06/2011	Metal ion levels[266]	Consolidated
PS110074	MicroPort	Profemur s hip stem	Orthopedic	05/06/2011	Metal ion levels[267]	Consolidated
PS110073	MicroPort	Conserve plus spiked acetabular shells and conserve total 56mm femoral head	Orthopedic	05/06/2011	Metal ion levels[268]	Consolidated
PS110072	MicroPort	Metal transcend articulation system (larger sizes)	Orthopedic	05/06/2011	Metal ion levels[269]	Consolidated
PS110071	MicroPort	Metal transcend articulation system	Orthopedic	05/06/2011	Metal ion levels[270]	Consolidated
PS110070	MicroPort	Metal transcend articulation system	Orthopedic	05/06/2011	Metal Ion Levels Microport[271]	Study Pending
					Explant[272]	Study Pending
					Metal Ion Levels Wright[273]	Revised/Replaced Study
PS110069	Stryker Orthopaedics for Howmedica Osteonics Corp.	Acetabular dome hole plugs	Orthopedic	05/06/2011	Metal ion levels[274]	Terminated
PS110068	Stryker Orthopaedics for Howmedica Osteonics Corp.	Acetabular dome and screw hole plugs	Orthopedic	05/06/2011	Metal ion levels[275]	Terminated
PS110067	Stryker Orthopaedics for Howmedica Osteonics Corp.	Omniflex normalized hip stem for press-fit fixat	Orthopedic	05/06/2011	Metal ion levels[276]	Terminated
PS110066	Stryker Orthopaedics for Howmedica Osteonics Corp.	(modified) omnifit threaded acetabular component	Orthopedic	05/06/2011	Metal ion levels[277]	Terminated
PS110065	Stryker Orthopaedics for Howmedica Osteonics Corp.	Micro-struc. Acetabular compon- mc2p	Orthopedic	05/06/2011	Metal ion levels[278]	Terminated
PS110064	Stryker Orthopaedics for Howmedica Osteonics Corp.	Omnifit threaded acetabular components 2005 series	Orthopedic	05/06/2011	Metal ion levels[279]	Terminated
PS110063	Stryker Orthopaedics for Howmedica Osteonics Corp.	Uhmwpe hip and knee components - packaging change	Orthopedic	05/06/2011	Metal ion levels[280]	Terminated
PS110062	Stryker Orthopaedics for Howmedica Osteonics Corp.	Pca acetabular insert ii, additional sizes, styles	Orthopedic	05/06/2011	Metal ion levels[281]	Terminated
PS110061	Stryker Orthopaedics for Howmedica Osteonics Corp.	Pca(r) solid back acetabula shell	Orthopedic	05/06/2011	Metal ion levels[282]	Terminated
PS110060	Stryker Orthopaedics for Howmedica Osteonics Corp.	Pca acetabular insert ii	Orthopedic	05/06/2011	Metal ion levels[283]	Terminated
PS110059	Stryker Orthopaedics for Howmedica Osteonics Corp.	Bg proximal femur	Orthopedic	05/06/2011	Metal ion levels[284]	Terminated
PS110058	Stryker Orthopaedics for Howmedica Osteonics Corp.	Total hip, lord madreporic	Orthopedic	05/06/2011	Metal ion levels[285]	Terminated
PS110057	Stryker Orthopaedics for Howmedica Osteonics Corp.	Prosthesis, vidal total hip	Obstetrics/ Gynecology	05/06/2011	Metal ion levels[286]	Terminated
PS110055	Johnson and Johnson	PROFILE FEMORAL HIP	Orthopedic	05/06/2011	Metal ion	Terminated

					levels[287]	
PS110054	Johnson and Johnson	Depuy pinnacle with gription acetabular cups	Orthopedic	05/06/2011	Metal ion levels[288]	Consolidated
					Explant Analysis[289]	Consolidated
PS110053	Johnson and Johnson	Depuy pinnacle 100 with gription acetabular cups	Orthopedic	05/06/2011	Metal ion levels[290]	Consolidated
					Explant Analysis[291]	Consolidated
PS110052	Johnson and Johnson	Depuy pinnacle metal-on-metal acetabular cup liners	Orthopedic	05/06/2011	Metal ion levels[292]	Consolidated
					Explant Analysis[293]	Consolidated
PS110051	Johnson and Johnson	Depuy c-stem amt	Orthopedic	05/06/2011	Metal ion levels[294]	Consolidated
					Explant Analysis[295]	Consolidated
PS110050	Johnson and Johnson	Depuy asphere m-spec head	Orthopedic	05/06/2011	Metal ion levels[296]	Consolidated
					Explant Analysis[297]	Consolidated
PS110049	Johnson and Johnson	Depuy asr 300 acetabular cup system	Orthopedic	05/06/2011	Metal ion levels[298]	Consolidated
					Explant Analysis[299]	Consolidated
PS110048	Johnson and Johnson	Depuy asr xl modular acetabular cup system	Orthopedic	05/06/2011	Metal ion levels[300]	Consolidated
					Explant Analysis[301]	Consolidated
PS110047	Johnson and Johnson	Depuy tri-lock bone preservation stem	Orthopedic	05/06/2011	Metal ion levels[302]	Consolidated
					Explant Analysis[303]	Consolidated
PS110046	Johnson and Johnson	Depuy corail amt dysplasia hip prosthesis	Orthopedic	05/06/2011	Metal ion levels[304]	Consolidated
					Explant Analysis[305]	Consolidated
PS110045	Johnson and Johnson	Depuy asr taper sleeve adapter	Orthopedic	05/06/2011	Metal ion levels[306]	Consolidated
					Explant Analysis[307]	Consolidated
PS110044	Johnson and Johnson	Depuy pinnacle metal-on-metal acetabular cup liners	Orthopedic	05/06/2011	Metal ion levels[308]	Consolidated
					Explant Analysis[309]	Consolidated
PS110043	Johnson and Johnson	Dupuy s-rom std hip stem prosthesis	Orthopedic	05/06/2011	Metal ion levels[310]	Consolidated
					Explant Analysis[311]	Consolidated
PS110042	Johnson and Johnson	Corail amt hip prosthesis	Orthopedic	05/06/2011	Metal ion levels[312]	Consolidated
					Explant Analysis[313]	Consolidated
PS110041	Johnson and Johnson	Depuy asr modular acetabular cup system	Orthopedic	05/06/2011	Metal ion levels[314]	Consolidated
					Explant Analysis[315]	Consolidated
PS110040	Johnson and Johnson	Depuy pinnacle metal-on-metal acetabular cup liner	Orthopedic	05/06/2011	Metal ion levels[316]	Consolidated
					Explant Analysis[317]	Consolidated
PS110039	Johnson and Johnson	Pinnacle metal-on-metal acetabular cup liners	Orthopedic	05/06/2011	Metal ion levels[318]	Consolidated
					Explant Analysis[319]	Consolidated
PS110038	Johnson and Johnson	Depuy pinnacle metal-on-metal acetabular cup liners	Orthopedic	05/06/2011	Metal ion levels[320]	Progress Adequate
					Explant Analysis[321]	Progress Adequate
PS110037	Johnson and Johnson	ULTIMA METAL-ON-METAL ACETABULAR CUP	Orthopedic	05/06/2011	Metal ion levels[322]	Other
PS110036	Encore Medical	Fmp metal/metal acetabular insert	Orthopedic	05/06/2011	Clinical Study[323]	Consolidated
					Device Retrieval Study[324]	Consolidated
PS110035	Encore Medical	Metal backed acetabular component	Orthopedic	05/06/2011	Clinical Study[325]	Consolidated
					Device Retrieval Study[326]	Consolidated
PS110034	Encore Medical	Djo surgical revision femoral hip system, model 428-14/24-140/200; 428-00-050/110	Orthopedic	05/06/2011	Clinical Study[327]	Consolidated
					Device Retrieval Study[328]	Consolidated
PS110033	Encore Medical	Revelation stem, model 427-21/42-080/180	Orthopedic	05/06/2011	Clinical Study[329]	Consolidated
					Device Retrieval Study[330]	Consolidated
PS110032	Encore Medical	Fmp metal/metal acetabular insert, 499-28,449-34, 499-38	Orthopedic	05/06/2011	Clinical Study[331]	Consolidated
					Device Retrieval Study[332]	Consolidated
PS110031	Encore Medical	Modification to: Fmp metal/metal acetabular insert, models 499-28, 499-34, 499-38	Orthopedic	05/06/2011	Clinical Study[333]	Consolidated

					Device Retrieval Study[334]	Consolidated
PS110030	Encore Medical	Metal/metal hip system	Orthopedic	05/06/2011	Clinical Study[335]	Consolidated
					Device Retrieval Study[336]	Consolidated
PS110029	DJO Global	Encore clp offset total hip system, metal/metal hip system,fmp metal/metal acetabular insert, revelation stem,djo surgical revision femoral i-lip system, metal backed acetabular component,	Orthopedic	05/06/2011	Clinical Study[337]	Progress Adequate
					Device Retrieval Study[338]	Progress Adequate
PS110026	Biomet Inc.	Ringloc + hybrid acetabular system	Orthopedic	05/06/2011	Metal Ion Levels[339]	Consolidated
PS110025	Biomet Inc.	Taper 2 porous femoral stem	Orthopedic	05/06/2011	Metal Ion Levels[340]	Consolidated
PS110024	Biomet Inc.	Balance hip system	Orthopedic	05/06/2011	Metal Ion Levels[341]	Consolidated
PS110023	Biomet Inc.	Biomet modular femoral revision system	Orthopedic	05/06/2011	Metal Ion Levels[342]	Consolidated
PS110022	Biomet Inc.	Biomet metal-on-metal hip systems- expanded contraindications	Orthopedic	05/06/2011	Metal Ion Levels[343]	Consolidated
PS110021	Biomet Inc.	Compress segmental femoral replacement system	Orthopedic	05/06/2011	Metal Ion Levels[344]	Consolidated
PS110020	Biomet Inc.	Porous coated acetabular components	Orthopedic	05/06/2011	Metal Ion Levels[345]	Consolidated
PS110019	Biomet Inc.	M2a/c2a acetabular system	Orthopedic	05/06/2011	Metal Ion Levels[346]	Consolidated
PS110018	Biomet Inc.	Mallory-head modular calcar stems with interlocking slots	Orthopedic	05/06/2011	Metal Ion Levels[347]	Consolidated
PS110017	Biomet Inc.	M2a magnum system	Orthopedic	05/06/2011	Metal Ion Levels[348]	Consolidated
PS110016	Biomet Inc.	M2a acetabular system	Orthopedic	05/06/2011	Metal Ion Levels[349]	Consolidated
PS110015	Biomet Inc.	M2a 28mm ringloc liner	Orthopedic	05/06/2011	Metal Ion Levels[350]	Consolidated
PS110014	Biomet Inc.	Metal on metal acetabular system	Orthopedic	05/06/2011	Metal Ion Levels[351]	Consolidated
PS110013	Biomet Inc.	Compress segmental femoral replacement system (short spindle and anchor plug)	Orthopedic	05/06/2011	Metal Ion Levels[352]	Consolidated
PS110012	Biomet Inc.	Parallel-sided extensively coated femoral stems	Orthopedic	05/06/2011	Metal Ion Levels[353]	Consolidated
PS110011	Biomet Inc.	Echo bi-metric press-fit stems	Orthopedic	05/06/2011	Metal Ion Levels[354]	Consolidated
PS110010	Biomet Inc.	Altra fx hip system	Orthopedic	05/06/2011	Metal Ion Levels[355]	Consolidated
PS110009	Biomet Inc.	Altra press-fit hip system	Orthopedic	05/06/2011	Metal Ion Levels[356]	Consolidated
PS110008	Biomet Inc.	M2a-magnum tri-spike acetabular component	Orthopedic	05/06/2011	Metal Ion Levels[357]	Consolidated
PS110007	Biomet Inc.	Lateralized taperloc microplasty femoral components	Orthopedic	05/06/2011	Metal Ion Levels[358]	Consolidated
PS110006	Biomet Inc.	M2a magnum 12/14 taper inserts and one-piece modular heads	Orthopedic	05/06/2011	Metal Ion Levels[359]	Consolidated
PS110005	Biomet Inc.	Porous titanium acetabular augments, m2a magnum 12/14 taper inserts and one-piece modular heads	Orthopedic	05/06/2011	Metal Ion Levels[360]	Progress Adequate
					Explant Analysis[361]	Completed
PS110004	Biomet Microfixation	Total temporomandibular joint replacement system	Dental	02/04/2011	Time to Revision[362]	Progress Adequate
					Explant[363]	Progress Adequate
PS110003	TMJ Concepts	Patient-fitted tmj reconstruction prosthesis system	Dental	02/04/2011	Time to Revision and Explant Analysis[364]	Progress Inadequate
PS110002	Nexus CMF	Tmj fossa-eminence/condylar prosthesis system	Dental	02/04/2011	Registry Database[365]	Revised/Replaced Study
					TMJ Fossa-Eminence and Condylar Pros[366]	Revised/Replaced Study
					TMJ Registry Study - Total[367]	Revised/Replaced Study
					TMJM Registry Study - Partial[368]	Revised/Replaced Study
					Prospective Postmarket Surveillance Study Plan [369]	Progress Inadequate
					Explant Analysis Study Plan [370]	Progress Adequate
PS110001	Vermillion, Inc	Ova1	Immunology	01/31/2011	OVA1 Performance in Pre and Post Menopausal Women[371]	Completed
PS100013	CareFusion	Smartsite needle free valve administration sets	General Hospital	07/21/2010	BSI rate[372]	Other
PS100012	CareFusion	Ivac needle free administration sets	General Hospital	07/21/2010	BSI rate[373]	Other
PS100011	Becton Dickinson Infusion Therapy Systems	Nima needleless injectionsite master adapter with posiflow positive displacement feature, and iv sets	General Hospital	07/21/2010	BSI rate[374]	Other
PS100010	CareFusion	Maxplus tru-swab positive displacement connector	General Hospital	07/21/2010	BSI rate[375]	Completed

PS100009	CareFusion	Maxplus tru-swab positive displacement connector	General Hospital	07/21/2010	BSI rate[376]	Completed
PS100008	Becton Dickinson Infusion Therapy Systems	Bd posiflow/tm positive displacement valve	General Hospital	07/21/2010	BSI rate[377]	Other
PS100007	Baxter Healthcare Corporation	Iv/catheter extension set with nac plus needleless access connector and nac plus needleless access connector	General Hospital	07/21/2010	BSI rate[378]	Other
PS100006	B. Braun Medical Inc.	Ultrasite valve	General Hospital	07/21/2010	BSI rate[379]	Completed
PS100005	ICU Medical, Inc.	Tego	General Hospital	07/21/2010	BSI rate[380]	Other
PS100004	ICU Medical, Inc.	Clc2000 catheter patency device	General Hospital	07/21/2010	BSI rate[381]	Other
PS100003	ICU Medical, Inc.	Clc2000	General Hospital	07/21/2010	BSI rate[382]	Other
PS100002	Amsino International, Inc	Cortez needle free iv connector	General Hospital	07/21/2010	BSI rate[383]	Other
PS100001	MicroVention, Inc.	Microvention hydrocoil-soft-frame	Neurology	04/15/2010	HydroCoil Study[384]	Completed
					HydroSoft/HydroFrame Study[385]	Progress Adequate
PS090017	Zimmer Spine	Zimmer® dynesys® top-loading spinal system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[386]	Terminated
PS090016	Zimmer Spine	Zimmer® dynesys® spinal system with dto implant	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[387]	Terminated
PS090015	Exactech, Inc.	Modified vertiflex spinal screw system (with dynabolt rods)	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[388]	Terminated
PS090014	Ulrich Medical USA	Cosmic system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[389]	Terminated
PS090013	Ulrich Medical USA	Sscs hinged screws	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[390]	Terminated
PS090012	Alphatec Spine	Isobar semi-rigid spinal system & dual dampener	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[391]	Terminated
PS090011	Paradigm Spine	Dss stabilization system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[392]	Terminated
PS090010	Synthes Spine	Ngarde system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[393]	Terminated
PS090009	Medtronic Sofamor Danek	Cd horizon® agile¿ dynamic stabilization device	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[394]	Terminated
PS090008	Medtronic	Cd horizon® peek rods	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[395]	Terminated
PS090007	Globus Medical, Inc.	Transition stabilization system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[396]	Terminated
PS090006	Globus Medical, Inc.	Protex rods	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[397]	Terminated
PS090005	DePuy Spine	6.35mm and 5.5mm peek rods	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[398]	Terminated
PS090004	Biospine Co., Ltd.	Bioflex®	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[399]	Terminated
PS090003	Applied Spine Technologies, Inc.	Bar pedicle screw spinal fixation system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[400]	Terminated
PS090002	Alphatec Spine	Zodiac dynamo semi-rigid spinal system	Orthopedic	10/05/2009	Fusion, AEs, Surg Procedures[401]	Terminated
PS090001	Szabocsik and Associates	Jsz orthokeratology contact lenses for overnight wear	Ophthalmic	08/07/2009	Microbial Keratitis[402]	Other
PS060003	Cardica, Inc.	C-port distal anastomosis system	Cardiovascular	06/14/2006	Graft Patency and Technical Failure[403]	Completed
PS060002	The Ohio State University	Paragon crt 100 lens and boston vision shaping treatment (vst) lens for ook	Ophthalmic	05/25/2006	Microbial Keratitis Study[404]	Completed
PS060001	Philips Medical Systems, Heartstream	Philips heartstart home otc defibrillator	Cardiovascular	12/07/2005	non-prescription use[405]	Completed
PS040001	ZOLL Circulation, Inc.	Alsius coolgard 3000/coolline catheter thermal regulation system	Neurology	03/05/2004	Mortality Study[406]	Completed
PS010001	Medtronic Vascular	Aneurx stent graft system	Cardiovascular	06/13/2001	AneuRx Stent Graft System[407]	Completed

- The 522 Postmarket Surveillance Studies Program encompasses design, tracking, oversight, and review responsibilities for studies mandated under section 522 of the Federal Food, Drug and Cosmetic Act. The program helps ensure that well-designed 522 postmarket surveillance (PS) studies are conducted effectively and efficiently and in the least burdensome manner.
- In May 2008, the oversight responsibility of the 522 Postmarket Surveillance Studies Program was transferred to the Division of Epidemiology (DEPI) of the Office of Surveillance and Biometrics (OSB)/Center for Devices and Radiological Health (CDRH). DEPI continues to build the 522 program.
- CDRH has established an automated internal tracking system that efficiently identifies the reporting status of active 522 PS studies based on study timelines incorporated in study protocols and agreed upon by the CDRH and applicants. This system represents CDRH's effort to ensure that all 522 PS commitments are fulfilled in a timely manner.
- In addition, CDRH launched this publicly available webpage to keep all stakeholders informed of the progress of each 522 PS study. The webpage displays general information regarding

each study, as well as the overall study status (based on protocol-driven timelines and adequacy of the data) and the applicant's reporting status for each submission due.

Links

- Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry and Food and Drug Administration Staff[408]
- 522 Webpage FAQs[409]
- Webinar Presentation - Announcing Final Guidance on Postmarket Surveillance Under Section 522 of the Food, Drug, and Cosmetic Act and FDA Webinar on the Final Guidance [410]
- Webinar Transcript - Announcing Final Guidance on Postmarket Surveillance Under Section 522 of the Food, Drug, and Cosmetic Act and FDA Webinar on the Final Guidance [411]

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Removing Retrievable Inferior Vena Cava Filters: FDA Safety Communication

This safety communication updates FDA's 2010 Initial Communication. The update provides information on recently published research and postmarket studies for these devices. There are no new safety concerns related to this update.

Date Updated: May 6, 2014

Date of Initial Communication: August 9, 2010 (https://wayback.archive-it.org/7993/20161022180008/http:/www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm221676.htm)

Audience: Physicians who implant inferior vena cava (IVC) filters and clinicians responsible for the ongoing care of patients with these devices.

Medical Specialties: Interventional radiology, interventional cardiology, vascular surgery, trauma care, bariatric surgery, orthopedic surgery, primary care

Device:
IVC filters are small, cage-like devices that are inserted into the inferior vena cava to capture blood clots and prevent them from reaching the lungs. The inferior vena cava is the main vessel returning blood from the lower half of the body to the heart. IVC filters are frequently placed in patients at risk for pulmonary embolism (a blood clot in the lungs) when anticoagulant therapy cannot be used or is ineffective. IVC filters are designed to be permanent implants although some of these devices may have the option to be removed.

Purpose: The Food and Drug Administration (FDA) is updating a previously issued Initial Communication to include information on recently published research and postmarket surveillance studies for these devices.

Summary of Problem and Scope:
The FDA has received reports of adverse events and product problems associated with IVC filters. Types of reports include device migration, filter fracture, embolization (movement of the entire filter or fracture fragments to the heart or lungs), perforation of the IVC, and difficulty removing the device. Some of these events led to adverse clinical outcomes. These types of events may be related to how long the filter has been implanted. Other known long-term risks associated with IVC filters include lower limb deep vein thrombosis and IVC occlusion. For patients with retrievable filters, some complications may be avoided if the filter can be removed once the risk of pulmonary embolism has subsided. The FDA is concerned that retrievable IVC filters, when placed for a short-term risk of pulmonary embolism, are not always removed once the risk subsides.

Recommendations/Actions:
The FDA recommends that implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection from pulmonary embolism is no longer needed.

The FDA encourages all physicians involved in the treatment and follow-up of patients receiving IVC filters to consider the risks and benefits of filter removal for each patient. A patient should be referred for IVC filter removal when the risk/benefit profile favors removal and the procedure is feasible given the patient's health status.

FDA Activities:
The FDA developed a quantitative decision analysis using publicly available data available in the medical literature to assess whether there is a time period during which the risk of having an IVC filter in place is expected to outweigh the benefits. The decision analysis (Decision Analysis of Retrievable Inferior Vena Cava Filters in Patients without Pulmonary Embolism) was published in the **Journal of Vascular Surgery: Venous and Lymphatic Disorders (/downloads/MedicalDevices/Safety/AlertsandNotices/UCM396384.pdf)** in October 2013. The mathematical model suggested that if the patient's transient risk for pulmonary embolism has passed, the risk/benefit profile begins to favor removal of the IVC filter between 29 and 54 days after implantation.

Although the results of the decision analysis provide important insight for retrievable IVC filters, the FDA is requiring collection of additional clinical data for currently marketed IVC filters in the United States. The studies will address safety questions that remain unanswered for both permanent and retrievable filters. Manufacturers were given two options for obtaining the data. Some manufacturers are participating in the **PRESERVE (http://evtoday.com/2012/10/preserve-trial-to-be-a-comprehensive-study-of-inferior-vena-cava-filters)** (PREdicting the Safety and Effectiveness of InferioR VEna Cava Filters) study, an independent national clinical study that will examine the use of IVC filters in the prevention of pulmonary embolism. Other manufacturers are conducting postmarket surveillance (**522 Studies (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pss.cfm)**). The data gathered from the PRESERVE study and the 522 studies will help the FDA, manufacturers and health care professionals assess the use and safety profile of these devices, understand evolving patterns of clinical use of IVC filters and ultimately improve patients care.

Contact Information:
If you have questions about this communication, please contact the Division of Industry and Consumer Education (DICE) at **DICE@cdrh.fda.gov (mailto:DICE@cdrh.fda.gov)** or 800-638-2041.

Resources

- **Decision Analysis of Retrievable Inferior Vena Cava Filters in Patients without Pulmonary Embolism (PDF - 553KB) (/downloads/MedicalDevices/Safety/AlertsandNotices/UCM396384.pdf)**
- **Decision Analysis of Retrievable Inferior Vena Cava Filters in Patients Without Pulmonary Embolism (Abstract) (http://www.jvsvenous.org/article/S2213-333X(13)00051-6/abstract) (/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)**
- **522 Postmarket Surveillance Studies (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm)**
- **PRESERVE Study to be Comprehensive Evaluation of Inferior Vena Cava Filter Use (Endovascular Today) (http://evtoday.com/2012/10/preserve-trial-to-be-a-comprehensive-study-of-inferior-vena-cava-filters) (/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)**

More in Safety Communications (/MedicalDevices/Safety/AlertsandNotices/default.htm)

2017 Safety Communications (/MedicalDevices/Safety/AlertsandNotices/ucm553873.htm)

2016 Safety Communications (/MedicalDevices/Safety/AlertsandNotices/ucm553855.htm)

EXHIBIT L

Second Supplement Expert Report

David A. Kessler, M.D.

Para. 44

To avoid duplication, Plaintiffs are not submitting the documents referenced in Foonote 24 to Paragraph of 44 of Dr. Kessler's Second Supplemental Expert Report. These documents were previously produced in Bard's Statement of Facts and Supporting Declarations.

510(k) applications: BPVE-01-00065938 (K970099); BPV-17-01-00057953 (K022236); BPV-17-01-00054947 (K031328); BPV-FULLER-00006046 (K050558); BPV-17-01-000131271 (K052578); BPV-17-01-00125963 (K062887); BPV-17-01-00123629 (K073090); BPV-17-01-00130268 (K080668); BPV-17-01-00131320 (K082305); BPVEFILTER-02-00042265 (K093659); BPV-17-01-00171679 (K101431); BPV-17-01-00150192 (K102511); BPV-17-01-00147141 (K112497); BPV-17-01-00213103, BPV-17-01-00213189, BPV-17-01-00213689, BPV-17-01-00214188, BPV-17-01-00214588, BPV-17-01-00215018, BPV-17-01-00215974, BPV-17-01-00216074, BPV-17-01-00216174, BPV-17-01-00216474, BPV-17-01-00216874, BPV-17-01-00217098 (K130366), and BPV-17-01-00217322 (K143208).